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NEUROPATHOLOGIC CHANGES ASSOCIATED WITH EXPERIMENTAL ANAPHYLAXIS IN THE MONKEY

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Although pathologic investigations on various tissues and organs of animals subjected to experimental anaphylaxis have been numerous, only a few papers can be found in the literature on morphologic changes of the nervous system due to anaphylactic reactions. Two of these papers are concerned with the pathologic changes associated with the Arthus phenomenon in the brain. Davidoff, Seegal and Seegal,[1] in rabbits prepared with multiple sensitizing injections of horse serum and shocked by one intracerebral injection, observed an extensive inflammatory lesion in the brain characterized by hemorrhage, edema, leukocytic infiltration and serum exudate. Alexander and Campbell[2] used a single intraperitoneal injection of horse serum in guinea pigs, followed by reinjection of the antigen intracerebrally. A lesion resulted characterized by "hemorrhage, vascular thrombosis, necrosis, demineralization, scavenger cells and reaction of microglia, oligodendroglia and astrocytes." These investigations leave little doubt as to the occurrence of a typical Arthus phenomenon in the brain of both rabbits and guinea pigs.

A few other papers are concerned with changes in the nervous system during generalized anaphylactic shock. In 1913 Rachmanow[3]

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1. Davidoff, L. M.; Seegal, B. C., and Seegal, D.: The Arthus Phenomenon: Local Anaphylactic Inflammation in the Rabbit Brain, J. Exper. Med. **55**:163, 1932.

2. Alexander, L., and Campbell, A. C. P.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229, 1937.

3. Rachmanow, M.: Lésions nerveuses dans l'anaphylaxie sérique et vermineuse, Compt. rend. Soc. de biol. **75**:317, 1913.

described degenerative alterations in the neuron cells of animals which had died in anaphylactic shock. Weinberg [4] in cases of severe shock found perivascular infiltration with round cells, hemorrhages, occasional thrombosis and diffuse degenerative changes in the neuron cells. He described, in addition, alterations of the myelin sheaths. Feuillié and Thiers [5] produced shock by injecting intravenously into a dog five doses of Witte's peptone (0.1 Gm. per kilogram of body weight) over a period of two weeks. Pathologically, there was lymphocytic infiltration of the pia at the level of the lumbar region but no changes in the nerve tissue proper. Stief and Tokay,[6] in guinea pigs, rabbits and dogs which died after anaphylactic shock, observed two types of diffuse lesions, vascular and parenchymatous. The former were essentially hemorrhagic and the latter degenerative. Garcin, Bertrand, Laplane and Frumusan [7] obtained no significant changes in the nervous system by repeated intravenous injections of horse serum. However, after repeated weekly injections of human serum in rabbits, 2 animals out of 5 showed changes characterized by neuronophagia, meningeal infiltrations and scattered microglia nodules. Similar lesions were obtained in the brain of guinea pigs in which human serum was repeatedly injected by the intraperitoneal route. Baginski, Czarnecki and Hurynowicz [8] sensitized and shocked 6 rabbits with horse serum injected by the intravenous and subcutaneous routes. Examination of the brain showed enlargement of the Robin-Virchow spaces and proliferation of adventitial cells. In addition, scattered throughout the brain, cerebellum and medulla were small necrotic foci, 0.04 to 0.1 mm. in diameter, consisting of necrotic nerve cells, proliferating microglia and occasional leukocytes and lymphocytes.

These investigations indicate that morphologic changes of the nerve tissue do occur in severe anaphylactic shock. However, the lack of specificity of the lesions described and the scantiness of histologic details in some reports make it difficult to evaluate these observations correctly.

The purpose of the present paper is to report on the pathologic changes in the central nervous system of monkeys in which anaphylactic

4. Weinberg, E.: Histologische Veränderungen in Gehirn während des anaphylaktischen Schocks, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:451, 1923.

5. Feuillié, E., and Thiers, J.: Production expérimentale de sclérose dans le système nerveux, Rev. neurol. **1**:606, 1926.

6. Stief, A., and Tokay, L.: Durch experimentelle Serumanaphylaxie verursachte Veränderungen des Nervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:715, 1934.

7. Garcin, R.; Bertrand, I.; Laplane, R., and Frumusan, P.: Sur certaines lésions histologiques du névraxe consécutives aux chocs anaphylactiques et aux injections réitératives espacées d'albumines étrangères chez l'animal, Compt. rend. Soc. de biol. **118**:1190, 1935.

8. Baginski, S.; Czarnecki, E., and Hurynowicz, J.: Lésions histologiques du système nerveux des lapins en état anaphylactique, Compt. rend. Soc. de biol. **130**: 567, 1939.

shock had been produced in various ways. The histologic features of a typical Arthus phenomenon in the monkey brain will be described. In addition, other types of lesions will be described which apparently have never been adequately reported in the literature on anaphylaxis. An interpretation of changes of the latter type will be attempted, based on a previously reported study [9] of similar lesions obtained after repeated subcutaneous injections of heterologous brain emulsion.

EXPERIMENTAL INVESTIGATION

The pathologic material consisted of the brains of 12 monkeys (Macacus rhesus). These animals had been the objects of extensive immunologic studies and reports by two of us (N. K. and L. M. K.).[10]

Experimental Data on Monkeys in Which Anaphylactic Shock Was Produced by Injections of Egg White

Monkey No.	Injection *	Interval Days	Injection	Interval Days	Injection	Interval Days	Injection	Interval Days	Injection	Interval Days	Injection
14	5 M†	15	1 V	15	1 C						
15	5 V†	15	1 V	15	1 C						
12	5 C†	15	1 V	15	5 C†	15	4 C†	15	1 C	45	V
20	3 C†	3	1 V	3	7 C†	15	7 C†	15	1 C	15	V
21	3 C†	3	1 V	3	7 C†	15	7 C†	15	3 C‖	30	2 V§
22	4 C‡	7	1 V	7	1 C‡	30	7 C‡	15	7 C‖	120	4 V§
23	4 C‡	7	1 V	7	6 C	30	7 C‡	15	7 C‖	120	1 V
11	5 C	15	1 V	15	1 V						
17	11 C‡	15	7 C	15	1 C	30	1 V	25	1 V		
43	11 C‡	21	25 C	15	12 C	18	6 C	24	6 C	30	6 C†
						30	11 C	30	9 C	90	1 V
45	11 C‡	21	25 C†	15	3 C†	18	6 C†				
46	11 C‡	30	27 C†	9	3 C†	18	6 C	180	9 M†	30	1 M

* C indicates intracerebral injection of 0.2 cc. of antigen; V, intravenous injection of 10 cc. of antigen (unless otherwise stated), and M, intramuscular injection of 0.2 cc. of antigen.
† At 2 day intervals.
‡ At weekly intervals.
‖ At about 1 month intervals.
§ 1 cc. at 15 day intervals.

With all of the animals under discussion the antigen used was egg white. Administration was by the intravenous, intramuscular and intracerebral routes. For the intracerebral injection, the brain was exposed, under aseptic conditions, through a small trephine hole. A needle (18 gage) was introduced into the hemisphere, lateral movement being avoided in order to reduce to a minimum any traumatic lesion of the brain matter. The antigen was injected slowly. All injections into the brain were made so far as possible at the same site.

The animals may be divided into four groups (table).

Group 1.—Two monkeys (14 and 15) were given five doses of 0.2 cc. of egg white at two day intervals by the intramuscular and the intravenous route,

9. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195 (Feb.) 1940.

10. Kopeloff, N.; Davidoff, L. M., and Kopeloff, L. M.: General and Cerebral Anaphylaxis in the Monkey (Macacus Rhesus), J. Immunol. **30**:6, 1936. Kopeloff, L. M., and Kopeloff, N.: Anaphylaxis in the Rhesus Monkey: I. Horse Serum as an Antigen, ibid. **36**:83, 1939; II. Egg-White as an Antigen, ibid. **36**:101, 1939.

respectively. After an interval of two weeks both animals received an intravenous injection of 10 cc. of the same antigen. Symptoms of collapse developed, but the animals recovered shortly. Two weeks later 0.2 cc. of antigen was injected intracerebrally. Monkey 14 showed convulsions and paretic symptoms on the side opposite that of the intracerebral injection. These lasted for six days; on the sixth day the animal died. Monkey 15 died within fifteen hours after the intracerebral injection, with severe symptoms of collapse. Both these animals received, as a control, 0.2 cc. of horse serum injected into the hemisphere on the side opposite that of the injection of antigens.

Group II.—A series of 5 monkeys (12, 20, 21, 22 and 23) received varying numbers of intracerebral and intravenous injections of antigen, as shown in the table. Three of these monkeys (12, 20 and 23) died within a few minutes after the last intravenous injection of antigen, while monkey 21 died two days later. In monkey 22 the intravenous administration of antigen did not have a fatal effect, and the animal was killed seven months after the last injection of antigen. All the animals of this group showed clinical signs of motor deficiency or motor irritation on the side opposite the intracerebral injections. These symptoms were first observed after the intracerebral injections which followed the first intravenous administration of antigen.

All the animals of this group received about the same number of injections of unrelated proteins in the cerebral hemisphere of the opposite side. This was done in order to study the morphologic differences between the local reaction produced by the antigenically active substance and that due to indifferent proteins.

Group III.—A series of 3 monkeys (11, 17 and 43) were given varying numbers of intracerebral injections of antigen at different intervals, followed by a shocking intravenous dose of the same antigen. Doses and intervals are shown in the table. All of the animals in this group died in collapse within a few minutes after the intravenous injection of antigen. During the course of treatment they all showed symptoms of involvement of the central nervous system consisting of more or less transient motor impairment, clonic movement, tremors, and the like, on the side opposite that on which the intracerebral injections were made. These symptoms appeared after from twelve to twenty-five intracerebral injections. In order to have a control for the local reaction to the antigen, monkey 17 was given the same number of injections of unrelated protein in the opposite cerebral hemisphere.

Group IV.—This group includes 2 monkeys (45 and 46) which received a large number of intracerebral injections of antigen into the same region of the brain. The number of injections and the intervals are shown in the table. Monkey 46 received, during the last months, two intravenous injections of antigen. The dose was not large enough, however, to cause a fatal shock, such as was produced in the monkeys of group III. This animal was eventually killed two weeks after the last injection. Monkey 45 did not receive any intravenous injection of antigen but was fed five times with 50 cc. of egg white during the last weeks, without apparent untoward effects. Both these animals showed signs of involvement of the central nervous system on the side opposite that of the injections, similar in character to those shown by the animals in group II and III.

PATHOLOGIC CHANGES

For the histologic study of the brain the usual methods of neuropathologic technic were employed.

A brief description of the principal pathologic lesions in each monkey will be presented, in the order given in the table.

GROUP I: *Monkey* 14.—In the left temporoparietal region, where the intracerebral injection of antigen was made, there appeared grossly a large necrotic hemorrhagic lesion, oval and measuring 25 by 12 mm. It involved the major part of the parietal and temporal lobes and the posterior third of the frontal lobe. The whole hemisphere appeared swollen, and the ventricular system had shifted toward the opposite side (fig. 1). On microscopic examination, the tissue in the center of the lesion appeared necrotic, myelin, axis-cylinders and glia cells being no longer recognizable. Within the meshwork of a loosened glia reticulum there was a large number of compound granular corpuscles, erythrocytes, lymphocytes and leukocytes (some of which were eosinophilic). Throughout the altered area

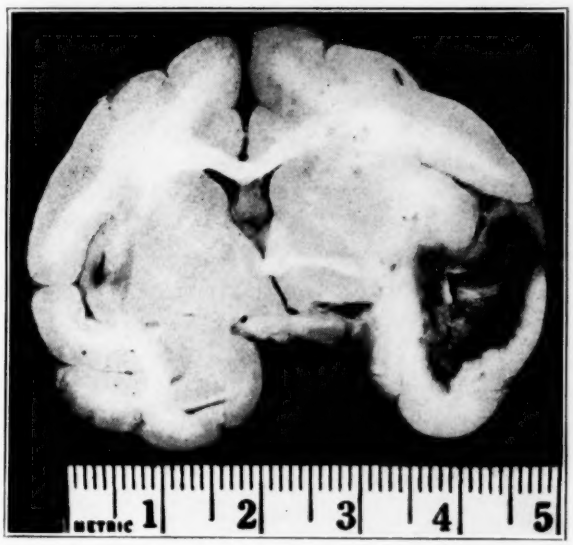

Fig. 1 (monkey 14).—Cross section showing the gross pathologic features of the Arthus phenomenon in the monkey brain.

the blood vessels were damaged, showing dilatation and necrotic walls. Numerous thrombosed vessels could be seen in Masson preparations. At the periphery of the lesion only the myelin was destroyed and the demyelinated tissue was filled with gitter cells. In the tissue surrounding the lesion there was considerable perivascular infiltration consisting of hematogenous elements and a few gitter cells. The vessels appeared markedly congested, and the tissue was edematous. Over the damaged tissue the pia was edematous and contained a large number of lymphocytes and leukocytes.

Examination of other regions of the central nervous system, including the right hemisphere, brain stem and cerebellum showed no significant changes except in the control lesion produced by injection of horse serum. This consisted of a small necrotic area, 5 by 2 mm. At the periphery there were numerous gitter cells and a few hematogenous elements, while in the center there was a loose reticulum in which single elements could hardly be recognized.

Monkey 15.—The right hemisphere, where the injection of antigen was made, showed a striking gross lesion consisting of numerous multiple hemorrhages which extended throughout the entire hemisphere and infiltrated the pia and the

Fig. 2 (monkey 15).—Cortex of the brain (frontal lobe) showing numerous hemorrhages, characteristic of the Arthus phenomenon in the monkey brain. Hematoxylin and eosin stain; low power.

cortical gray matter. On microscopic examination, the subpial spaces from the right frontal pole to the cerebellum were infiltrated with blood. The gray matter of the cortex and, to a less extent, of the lenticular nucleus, showed innumerable petechiae (fig. 2). On many occasions, adjacent petechiae had apparently fused

to form a larger hemorrhagic area. In the Masson preparation the vessel walls often appeared broken and typical thrombi could be occasionally seen within the lumen of the vessel. The perivascular tissue, where hemorrhage had occurred, was obviously altered, but no compound corpuscular elements were observed in the Herxheimer preparation. This diffuse hemorrhagic lesion was the only significant finding in this case. An injection of horse serum (0.2 cc.) was made into the left hemisphere at the time when the antigen was injected into the right hemisphere. No hemorrhagic lesion resulted; only a small necrotic area, 3 mm. in diameter, was observed.

GROUP II: *Monkey* 12.—A large necrotic lesion was observed in the parietal lobe of the right side corresponding with the site of injection of antigen. The lesion, irregular in outline, involved the entire lobe and measured 18 by 10 mm. During the process of embedding and staining the central part sloughed off for a diameter of 8 mm.; the remainder of the lesion was made up of a large number of scavenger cells and a few lymphocytes. At the periphery of the lesion numerous blood vessels were abundantly infiltrated with gitter cells, lymphocytes and leukocytes. The entire white matter of the right hemisphere, including the temporal and frontal lobes, showed irregular demyelination and an accumulation of compound granular corpuscles. The distribution of destroyed myelin sheaths was diffuse, but regional accentuation of the process was observed here and there around blood vessels. Subpial hemorrhages were present in some sections of the right hemisphere, particularly over the parietal and temporal lobes.

In the left hemisphere there was a multilocular necrotic cavity, measuring about 8 mm. in its largest diameter. There were a great number of perivascular demyelinated lesions scattered throughout the white matter, consisting mainly of gitter cells, a few lymphocytes and leukocytes. In some lesions characteristic giant cells, showing numerous nuclei and abundant cytoplasm filled with fat droplets, were occasionally observed. The cerebellum, pons and medulla presented no significant changes.

Monkey 20.—In the left parietal lobe, the site of injection of antigen, the entire white matter was altered, the myelin sheaths had almost completely disappeared, the axis-cylinders were partly broken down and a large number of cells, mainly compound granular corpuscles, filled the lesion. The demyelinated area contained several necrotic foci, 1 to 2 mm. in diameter (fig. 3), where the tissue had partially sloughed off. Almost all blood vessels within the lesion showed perivascular infiltration with gitter cells and hematogenous elements. As in the brain of the preceding monkey, there was partial demyelination extending to the frontal and temporal lobes.

The right cerebral hemisphere showed a few very small necrotic foci, about 0.5 mm. in diameter. The centrum semiovale was partially demyelinated, and numerous gitter cells, either diffusely distributed in the tissue or collected around blood vessels, could be observed. The parietal and temporal lobes were the most involved, while in the frontal and occipital lobes the lesions were only perivascular. There were a few giant cells and leukocytes within the latter. Examination of the midbrain, cerebellum, pons and medulla showed numerous perivascular lesions scattered throughout the white matter. Within these lesions the myelin appeared destroyed and a large number of cells filled the demyelinated area. Several lesions were made up almost exclusively of lymphocytes, plasma cells and polymorpho-

nuclear leukocytes, which were clearly of the eosinophilic type. In other lesions these hematogenous elements were mixed with gitter cells. Giant cells were not present.

Fig. 3 (monkey 20).—White matter of the parietal lobe showing partial necrosis of the tissue and thickening of the vessel walls. Hematoxylin and eosin stain; low power.

Monkey 21.—The cerebral changes in this monkey were similar to those in the preceding animal. However, the necrotic lesion at the site of the injection of antigen was less extensive. In the opposite hemisphere several perivascular foci of demyelination involved the internal capsule and a few other foci were irregularly scattered throughout the white matter. Within these lesions the myelin appeared destroyed and a large number of cells filled the demyelinated area. Several lesions were made up almost exclusively of lymphocytes, plasma cells and polymorphonuclear leukocytes. The last-mentioned cells were clearly of the eosinophilic type. In other lesions, these hematogenous elements were mixed with gitter cells. Giant cells were not present.

In comparing the largest necrotic focus due to the injection of antigen with the largest necrotic focus due to the injection of indifferent proteins, it was found that the former was about four times as extensive as the latter. However, no qualitative differences could be observed in the histologic features of the two foci.

Perivascular lesions similar to those observed in the brain of the preceding monkey were seen in the hypothalamus, while the medulla and pons were apparently normal. In the cerebellum a few gitter cells were occasionally found surrounding the small blood vessels and capillaries. No giant cells were observed in this case.

Monkey 22.—The local lesion in the left hemisphere where the local injections had been made was more extensive than those in the other animals of this group. The whole hemisphere was pierced with numerous necrotic foci of varying sizes, which in Nissl and hematoxylin and eosin preparations appeared to be made up of very loose glia and connective reticulum, tissue debris, erythrocytes and a few leukocytes and gitter cells. The few remaining blood vessels within the necrotic tissue had very thick walls, and often the lumen was obliterated. The nerve tissue outside the necrotic foci was extensively altered, showing demyelination and perivascular infiltration with gitter cells, and hematogenous elements.

In the right hemisphere, in which sixteen injections of unrelated proteins had been made, there were two small cystic cavities, 3 mm. in diameter. The tissue adjacent to the cysts contained a few gitter cells and numerous perivascular infiltrations, mainly of the hematogenous type.

Examination of other parts of the brain showed nothing of significance.

Monkey 23.—In the right hemisphere, where the injection of antigen had been made, the lesion was similar to that in monkey 22, although less extensive. There were multiple necrotic foci involving the entire parietal lobe. The lesion of the left hemisphere, where the control injections had been made, contained a small necrotic area, 3 mm. in diameter. Small perivascular lesions consisting of compound granular cells were occasionally seen in the occipital lobe of the left hemisphere and in the cerebellum.

GROUP III: *Monkey* 11.—In the left frontal lobe, the site of injection of antigen, the white matter appeared altered over an area approximately 7 mm. in diameter. Both myelin and axis-cylinders were destroyed, and gitter and glia cells were very numerous toward the periphery of the lesion. Polymorphonuclear leukocytes and lymphocytes were also seen in the altered tissue. In the left temporal lobe several lesions were observed consisting of numerous layers of gitter cells and occasional lymphocytes and giant cells of the type already described. The majority of these lesions were perivascular in distribution. However, a few appeared to be independent of the blood vessels. In the centrum semiovale of the right hemisphere there were a few very small perivascular lesions consisting of one or two layers of gitter cells.

There were no lesions in other parts of the brain.

Monkey 17.—On the left side, where the antigen was injected, two adjacent necrotic lesions, about 3 by 5 mm., involved the frontoparietal region. Microscopically, the necrotic area showed the same features as those observed in the other

Fig. 4 (monkey 17).—Numerous perivascular infiltrations of gitter cells, lymphocytes and leukocytes in the pons. Nissl stain; low power.

animals. However, the tissue adjacent to the lesion, including almost the entire centrum semiovale, was greatly altered. The myelin sheaths were partially destroyed, and a large number of gitter cells, both free in the tissue and collected around blood vessels, filled the areas of demyelination. Only occasionally were a few lymphocytes and leukocytes found in the perivascular infiltration.

In the right centrum semiovale a similar lesion was observed, although of a lesser degree of severity. The demyelination extended to the entire parietal and temporal lobes, while in the frontal and occipital lobes numerous small perivascular lesions made up of gitter cells were observed. The corpus callosum was also partially demyelinated and contained numerous gitter cells.

In the pons and the molecular layer of the cerebellum there were numerous small foci, mainly perivascular in distribution, which were made up of gitter cells and a few lymphocytes (fig. 4).

Monkey 43.—The left hemisphere, where the injections of antigen were made, showed a necrotic lesion at the level of the temporoparietal region. This lesion, measuring 7 by 10 mm. in its largest section, exhibited the microscopic features already observed in the animals of group II, but the tissue adjacent to the necrotic lesion was demyelinated only to a slight extent. Sections throughout the right hemisphere showed no significant changes except for a few gitter cells occasionally gathered around small blood vessels. Examination of the cerebellum and medulla revealed nothing abnormal. In the pons several foci were observed consisting of perivascular demyelination and infiltration with gitter cells.

GROUP IV: *Monkey* 45.—The left hemisphere, where the antigen had been injected, contained a necrotic lesion about 6 mm. in diameter, showing the usual pathologic features of a necrotic center and peripheral demyelination. The extent of the latter, however, was limited. The striking feature in this case was the presence of a large number of lesions, partly perivascular and partly without connection with blood vessels (fig. 5). They consisted of gitter cells, hematogenous elements and large giant cells (fig. 6), variously mingled. Foci consisting exclusively of gitter cells were numerous, while those showing only hematogenous cells were rare. These foci were frequently observed in the cerebellum, the pons, the medulla and the midbrain, while they were only occasionally found in the centrum semiovale. The foci involved the white matter exclusively.

Monkey 46.—The lesions in this animal were similar to those in monkey 45. There were a necrotic lesion in the left hemisphere, about 5 mm. in diameter, and a large number of foci in the pons and cerebellum. The necrotic lesion contained little fat and a large amount of proliferating glia. The majority of foci were characteristically perivascular and were made up of gitter cells. A few of them showed giant cells.

In summary, two main types of lesions were recognized. The first included the local reaction at the site of injection of antigen and was essentially characterized by necrosis of the tissue. In the center of the lesion all the elements of the tissue appeared to be destroyed; at the periphery the myelin sheaths were chiefly involved, the axis-cylinders and glia being better preserved. The blood vessels within the necrotic lesion exhibited thickening of the walls, thrombosis and obliteration of the lumen by connective tissue. Gitter cells, leukocytes and lymphocytes were frequently seen following perivascular infiltrations at the periphery of the lesion and scattered in the necrotic center. In the more advanced

lesions the necrotic center was transformed into a pseudocystic formation, and trabeculae of dense connective tissue and glia were observed among the tissue debris.

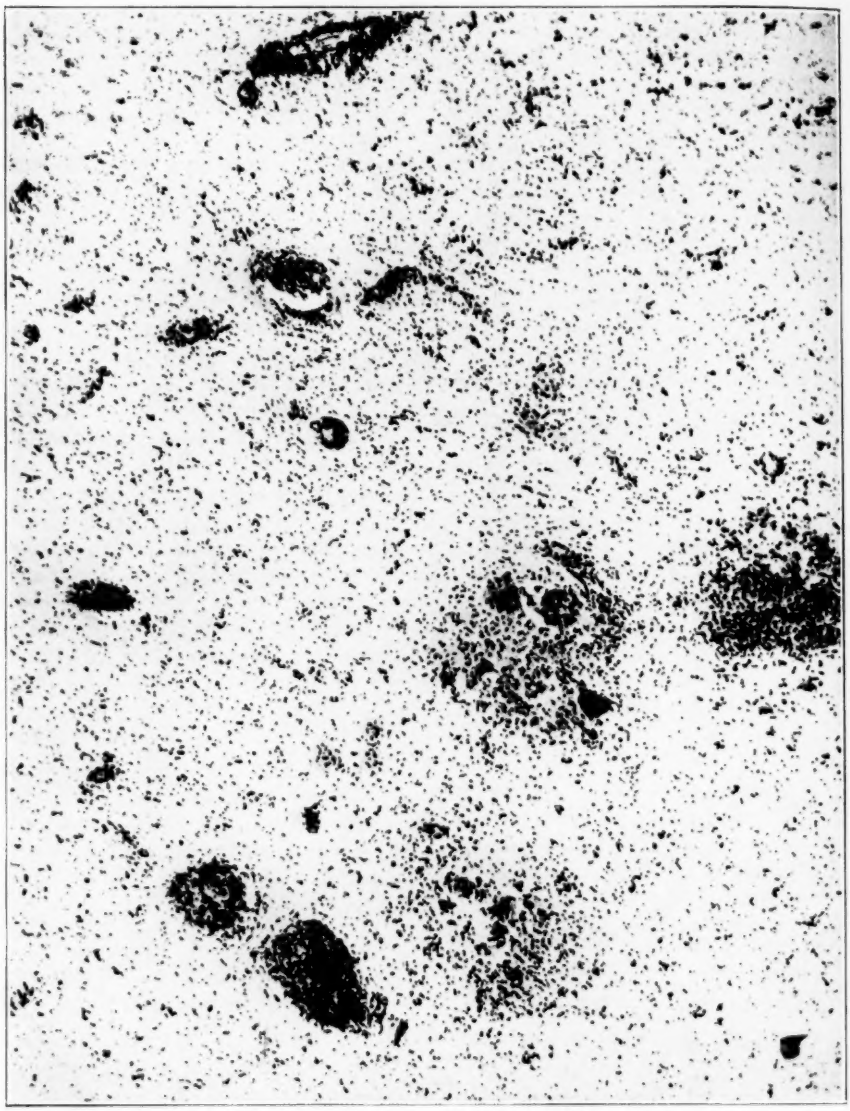

Fig. 5 (monkey 45).—Circumscribed lesions in the midbrain consisting of gitter cells, hematogenous elements and giant cells. Nissl stain; low power.

The second type of reaction included lesions in other parts of the brain. These consisted of circumscribed foci disseminated throughout both the white matter of the hemisphere opposite that containing the

local reaction and the white matter of the midbrain, cerebellum, pons and medulla. As shown with cellular stains, the lesions consisted of an accumulation of cellular elements, among which several types could be

Fig. 6 (monkey 45).—Similar lesions in the cerebellum containing numerous giant cells. Nissl stain; low power.

identified, including compound corpuscle elements laden with fat, lymphocytes, plasma cells, polymorphonuclear leukocytes (many of which appeared to be eosinophilic) and peculiar giant cells containing numer-

ous nuclei. Lesions consisting exclusively of gitter cells were the most often encountered; those consisting of numerous gitter cells and a few hematogenous elements were next in frequency. Lesions consisting exclusively of hematogenous elements were rare. Giant cells were present mainly in the foci consisting largely of gitter cells. In the myelin preparations the lesion appeared as a demyelinated area, usually fairly well defined. In the central part of the lesion there was often a blood vessel, usually a small vein. The blood vessels showed neither significant alteration of the intima or media nor thrombosis.

In addition to these circumscribed lesions, larger foci should be mentioned the main histologic features of which were the same, namely, demyelination and proliferation of gitter cells. However, these foci were more diffuse, extending occasionally over a large part of the centrum semiovale.

This separation of lesions into two main types was generally sharp. Thus, the lesions at the site of injection were always of the first type, while those in the midbrain, cerebellum, pons and medulla were always of the second type. However, in the neighborhood of the local lesion at the site of injection changes were occasionally observed the classification of which into one or the other type remained unsettled.

COMMENT

Since the pathologic changes in the nervous system may be divided into two main types, namely, a local lesion at the site of the intracerebral injection of antigen and lesions in other parts of the brain, each type will be discussed separately.

1. The local lesion at the site of the intracerebral injection of antigen in the monkeys of group I may be regarded as a typical Arthus phenomenon produced in the monkey brain. In fact, the experimental production of such a phenomenon, namely, sensitization by either the intravenous or the intramuscular route followed after a certain interval by local injection of the antigen, had previously been observed. In 1 case the local lesion was of extreme severity: Two-tenths cubic centimeter of antigen produced necrosis extending for a diameter of over 10 mm. and characterized by edema, hemorrhages, leukocytic infiltration and destruction of the tissue proper, including myelin sheaths, axis-cylinders and glia. In the other monkey of group I, hemorrhagic lesions dominated the pathologic picture. These lesions were of extreme severity, extending throughout the whole hemisphere and destroying large portions of the gray matter. The animal died within a few hours, a fact which explains the scarcity of tissue necrosis at the site of injection.

When the differences in the fundamental structures of the nerve tissue are taken into consideration, it will be seen that no significant deviation from the Arthus phenomenon observed in other viscera can be recognized as far as the quality of the lesion is concerned. As a matter of fact, necrosis of the tissue, edema, hemorrhages and perivascular infiltration with hematogenous cells are the common characteristics of the Arthus phenomenon in all parts of the body. Moreover, the speed and intensity of the reaction, so characteristic of the Arthus phenomenon, were well exemplified in both animals. That there do occur quantitative differences in the severity of pathologic changes according to the tissue involved is a well known fact (Doerr [11]). On the basis of the present experiments, it seems that the brain should be considered among the tissues extremely susceptible to local anaphylactic reaction. Altogether, however, the results in these experiments confirm work already published,[12] merely extending to the monkey brain the data obtained in studies on rabbits and guinea pigs.

The local lesions in group II may also be regarded as the expression of an Arthus phenomenon, since in all the animals of this group, after a few intracerebral injections of antigen, a large sensitizing dose of antigen given intravenously was followed by numerous local injections of the same antigen. The experimental conditions of a repeated Arthus phenomenon were thus realized. The pathologic features, in fact, closely resembled those of monkey 14, although organization of the lesions had taken place, as evidenced by proliferation of glia and overgrowth of connective tissue. That the lesion was not due only to mechanical tearing of the tissue and consequent aseptic inflammation was indicated by a comparison of the lesion produced by injection of the antigen in one hemisphere with the lesion produced by injection of the same amount of unrelated protein in the opposite hemisphere. Qualitative differences could not be established beyond doubt, but it was definitely ascertained that the former lesion was at least three times as extensive as the latter.

The local lesion described in the animals of groups III and IV cannot be regarded as the expression of a typical Arthus phenomenon, since the animals had received no sensitizing dose of antigen by the intravenous route previous to the local injections. It will be noted that in the animals of these groups the local lesion was comparatively less severe than in the animals of group II. For example, in monkey 17 (group III) it was less extensive than that in monkey 23 (group II), although the former had received eighty-six local injections while the latter had received only twenty-four. It seems safe to conclude tenta-

11. Doerr, R.: Die lokale Anaphylaxie, Ztschr. f. Hyg. u. Infektionskr. **118:** 623, 1936.

12. Davidoff, Seegal and Seegal.[1] Alexander and Campbell.[2]

tively that the local lesions found in the animals of groups III and IV were due to mechanical tearing of the tissue by numerous repeated injections and consequent aseptic inflammation.

2. Lesions in other parts of the brain far from the local alteration produced by the injection of antigen were found in all the animals of groups II, III and IV. In the attempt to explain the pathogenesis of this type of lesion, a few possible mechanisms will be taken briefly into consideration.

The lesions might first be considered as representing the hyperergic response of the brain tissue to a general allergic state brought about by the intravenous administration of the antigen into the sensitized animal. That such responses do occur in the heart and the kidney has been maintained by some investigators,[13] who, however, failed to detect involvement of the nervous system. To be sure, Garcin [7] and Baginski [8] and their co-workers have described occasional small necrotic foci associated with general allergic states, but their descriptions are too scanty to permit of a comparison with the lesions observed in our cases. On the other hand, the histologic examination of the brain of 2 monkeys which died after general anaphylactic shock brought about by intravenous administration of massive doses of egg white showed no lesions of this type. It should be noted, in any event, that this explanation might be valid only for the animals of group II, which received two intravenous injections of antigen, and not for the animals of group III and IV, which received only one intravenous injection of egg white or none. Yet in these two groups the perivascular lesions were more pronounced and diffuse than in those in group II. It appears impossible, therefore, that the lesions are the result of a generalized allergic reaction.

A second hypothesis, namely, that small thrombi in the blood vessels might be the immediate cause of the tissue lesion, seems a reasonable one. It is well known, in fact, that formation of thrombi is considered by many investigators as a characteristic feature of anaphylactic reactions.[14] To be sure, there is the distinct possibility that thrombi are secondary to tissue necrosis. In addition, it should be noted that histologic features, such as hemorrhage, primary infiltration with hematogenous elements and severe alteration of blood vessels, which are considered characteristic of the thrombotic softening in the central nervous system, were lacking in the available preparations. Finally,

13. Vaubel, E.: Die Eiweissüberempfindlichkeit (Gewebshyperergie) des Bindegewebes, Beitr. z. path. Anat. u. z. allg. Path. **89**:374, 1932. Knepper, R.: Ueber die Lokalisierung der experimentellen allergischen Hyperergie, Virchows Arch. f. path. Anat. **296**:364, 1936.

14. Dietrich, A., and Schroeder, K.: Abstimmung des Gefassenendothels als Grundlage der Thrombenbildung, Virchows Arch. f. path. Anat. **274**:425, 1930.

a careful search for thrombi using the connective stains of Mallory and Masson failed to detect typical thrombi at any stage. Although Putnam [15] expressed the opinion that the absence of actual thrombi is not evidence against the thrombotic origin of softening, since thrombi may be completely reabsorbed in a comparatively short time, it appears safe to look for more convincing evidence in support of the hypothesis of thrombotic origin of these lesions. In any event, this hypothesis would explain only the immediate cause of the lesion, leaving unsolved the problem as to how thrombi originate.

In the attempt to explain these lesions, it is of significance to note that lesions bearing a striking similarity to those described here can be produced under entirely different experimental conditions. As described in a previous paper,[9] when monkeys are given repeated inoculations of sterile extracts and emulsions of rabbit brain, a progressive condition develops characterized by symptoms indicating widespread involvement of the central nervous system. On pathologic examination, these animals show disseminated perivascular lesions characterized by destruction of myelin, accumulation of fatty granular elements and giant cells. The features of this lesion do not differ morphologically, in our estimation, from those found in the experiments here reported.

In discussing the mechanism of production of those lesions, it was maintained, as the most likely hypothesis, that the pathologic changes in the brain were due to brain-specific antibodies, the reacting antigen being a lipoid contained in the ether-alcohol extract, activated by a protein contained in the emulsion of heterologous brain. A similar explanation may be advanced for the present experiments. As a matter of fact, the latent period between the injection and the occurrence of symptoms seems to indicate that some type of antibody may be involved in the pathogenesis of the lesion. Moreover, the presence within the lesion of a foreign protein and of lipoid material appears to confirm this possibility. Tentatively, the mechanism of the lesion may then be visualized as follows: The intracerebral injection produces some damage in the nerve tissue, as evidenced by the extensive local necrosis. The brain tissue, more particularly the myelin sheaths, which presumably contain a specific hapten group,[16] is acted on by egg white, which as a foreign protein substance is capable of acting as a *Schlepper*. The combination of hapten and *Schlepper* produces a "complete antigen." The

15. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and Encephalomyelitis, Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

16. Schwentker, F. F., and Rivers, T. M.: The Antibody Response of Rabbits to Injections of Emulsion and Extracts of Homologous Brain, J. Exper. Med. **60**: 559, 1934.

damaged brain tissue being eventually absorbed by the body, complete antigens enter into the general circulation and thus may produce brain-specific antibodies [16] which will in turn react on the brain tissue, giving rise to the pathologic picture described here. It will be noted that the antibodies, being specific to the hapten group of the antigen, would theoretically react specifically on the myelin sheaths. This is what actually was observed, the lesion being always in the white matter and involving mainly the myelin sheaths.

The exact nature of this antigen-antibody reaction is still unknown. That it may be anaphylactoid in character has been claimed by Burky.[17] The presence of numerous eosinophilic leukocytes in the present cases seems to confirm this hypothesis from a purely pathologic point of view. On the other hand, if one assumes that thrombosis is the immediate cause of the lesion, the possibility that the antigen-antibody reaction might be operating through a vascular mechanism should be kept in mind. As a matter of fact, it has been claimed that the endothelium of blood vessels is susceptible to hyperergic inflammation [18] and that thrombosis is the result of damage of the endothelium due to an antigen-antibody reaction within the endothelial cells.[19]

In conclusion, both the pathologic changes in the brain previously recorded and those described in the present paper may be similarly explained on the assumption that brain-specific antibodies are responsible for the lesions. In the latter experiments the hapten is represented by altered homologous brain tissue, while in the former the hapten group consisted of heterologous brain substance. The fact that a heterologous protein was present in both types of experiments will hardly offer an explanation as to how such a mechanism could be operating in man. In the attempt to pursue the investigation still further, experiments are at present in progress designed to produce similar lesions of the brain under conditions which are presumably present in human pathologic states.

SUMMARY

The pathologic changes in the central nervous system of monkeys in which anaphylactic shocks had been produced in various ways are described.

17. Burky, E. L.: Production in Rabbit of Hypersensitive Reactions to Lens, Rabbit Muscle and Low Ragweed Extractions by Action of Staphylococcus Toxin, J. Allergy **5**:466, 1934.

18. Metz, W.: Die geweblichen Reaktionerscheinungen an der Gefässwand bei hyperergischen Zuständen und deren Beziehungen zur Periarteritis nodosa, Beitr. z. path. Anat. u. z. allg. Path. **88**:17, 1932. Apitz, K.: Ueber anaphylaktische Organveränderungen bei Kaninchen, Virchows Arch. f. path. Anat. **289**:46, 1933.

19. Opie, E. L.: Pathogenesis of the Specific Inflammatory Reaction of Immunized Animals, J. Immunol. **9**:259, 1924.

In brains of animals in which the experimental conditions for the occurrence of the Arthus phenomenon were realized, extensive foci of hemorrhagic necrosis were observed at the site of the injection of the shocking dose. These lesions showed essentially the same features as those observed in the Arthus phenomenon in other tissues.

A second type of lesion was observed in 10 monkeys which were given either a varying number of intracerebral and intravenous injections of antigen or only intracerebral injections. These lesions were scattered throughout the central nervous system and consisted of foci of demyelination, often perivascular in character. Within the foci, scavenging cells, lymphocytes, leukocytes and peculiar giant cells were observed. In discussing the pathogenesis of this type of lesion, the hypothesis is advanced that the damaged tissue in combination with the foreign protein produces brain-specific antibodies, which bring about the pathologic changes.

DISCUSSION

DR. L. S. KING, Princeton, N. J.: It is of interest that Muckenfuss recently showed that intracerebral injections of india ink into monkeys resulted in widespread distribution of the ink throughout the ventricular system and the subarachnoid space. Here the lesions following a single shocking dose of antigen are sharply circumscribed. When there were multiple intracerebral injections, could the diffuse damage be related to diffusion of the antigen, comparable to what Muckenfuss showed with india ink?

DR. G. A. JERVIS, New York: In no instance were the lesions predominant in the subarachnoid spaces or the periventricular regions. The lesions were usually perivascular in distribution. It seems therefore that Muckenfuss' experiments do not help in clarifying the pathologic picture described here.

ALTERED CONCEPT OF THERAPY OF INVOLUTIONAL MELANCHOLIA WITH ESTROGEN AND ANDROGEN

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Because of the usual temporal relationship between the menopause and the development of involutional psychoses, there has long been a tendency to link the two conditions in a causal relationship. The organic changes producing the clinical syndrome of the menopause have been thoroughly investigated, and it is now believed that the modus operandi is an exaggerated function of the pituitary resulting from ovarian failure, which can be demonstrated by an increased urinary excretion of gonadotropin. The clinical syndrome itself consists mainly in nervousness, headache, lassitude and depression, insomnia, irritability, hot flashes and various other vasomotor phenomena. Although one may be tempted to correlate some of these symptoms in their aggravated forms with the psychotic melancholia, it is by no means generally agreed that such a physiologic disturbance plays an etiologic role in the development of involutional psychoses.

Endocrine derangement in involutional melancholia should be demonstrable objectively in a manner similar to that of the menopausal syndrome. Saethre [1] found an increased urinary output of gonadotropin in a large group of patients with melancholia, and Jones and others [2] reported "positive" findings in the urine of over 60 per cent of women with psychotic depressions occurring at the menopause. Confirmatory evidence is also found in the work of Harris, Brand and Hinsie,[3] who observed, furthermore, that patients with the more marked

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1. Saethre, H.: Ueber die Ausscheidung von Prolan im Harn in der Involutionsperiode bzw. im Senium. Untersuchungen an normalen und psychiatrischem Material, Klin. Wchnschr. **12**:1727 (Nov. 4) 1933.

2. Jones, M. S.; MacGregor, T. N., and Todd, H.: Estradiol Benzoate Therapy in Depressions at Menopause, Lancet **1**:320 (Feb. 6) 1937.

3. Harris, M.; Brand, E., and Hinsie, L.: Studies of Urinary Excretions of Gonadal Stimulating Substance in Mental Patients, Am. J. Psychiat. **91**:1239 (May) 1935.

mental disturbance excreted the larger quantities of follicle-stimulating substance. Such evidence permits at least the conclusion that there is frequently a coexisting endocrine imbalance in involutional melancholia which in its objective manifestations seems identical with that of the menopausal syndrome.

Cessation of gonadal activity and subsequent hormonal imbalance are produced artificially by castration, and one might expect a psychotic condition similar to melancholia to develop in such persons. On the contrary, the literature, while rather scanty, fails to bear out this assumption. In a series of 112 castrated women Gordon [4] was unable to detect any true psychosis, and Corscaden [5] obtained similar results in a study of 148 women who had undergone radiotherapeutic menopause. In a discussion of the question, Codet [6] stated that cases of psychoses following castration, although reported, are not common and occur mostly in persons predisposed to the development of mental disease.

In any clinical consideration of typical involutional melancholia one is profoundly impressed by the uniformity and similarity of the patients' historical backgrounds. The personality prior to the onset of psychosis presents certain characteristic features which have been aptly described by the term "rigidity." Throughout their lives such persons are usually very sensitive and meticulous, devoid of humor, penurious and strikingly lacking in sexual drive. They are extremely inhibited, overly conscientious and strongly religious. This prepsychotic personality has been well discussed by Noyes [7] and more recently emphasized by Palmer and Sherman.[8] The latter investigators expressed the opinion that involutional melancholia is simply a phase in the life history of the patient, representing the culmination of a lifelong psychobiologic process of a distinct nature.

The elucidation of the relation of a prepsychotic personality to a subsequent psychosis marks an important milestone in the development of knowledge concerning this disease. Nevertheless, peculiar personality patterns may be found in practically all types of so-called functional psychoses and can hardly be regarded as the *sine qua non* without complete exploration of the pathophysiologic factors.

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4. Gordon, A.: Nervous and Mental Disturbances Following Castration in Women, J. A. M. A. **63**:1345 (Oct. 17) 1914.

5. Corscaden, J.: Radiotherapeutic Menopause: Its Significance and Management, Am. J. Obst. & Gynec. **11**:803 (June) 1926.

6. Codet, H.: Troubles psychopathiques de la castration féminine, Ann. méd.-chir. **2**:86 (April) 1937.

7. Noyes, A.: Modern Clinical Psychiatry, Philadelphia, W. B. Saunders Company, 1934.

8. Palmer, H. D., and Sherman, S. H.: The Involutional Melancholia Process, Arch. Neurol. & Psychiat. **40**:762 (Oct.) 1938.

If the cessation of ovarian activity and its resultant pituitary hyperfunction constitute an important factor in the development of involutional psychosis, it would seem logical to expect some measure of benefit in this disease from appropriate substitution therapy. In recent years a considerable number of reports have appeared in the literature regarding the use of estrogen in the treatment of involutional melancholia. Unfortunately, these are at extreme variance with each other, some investigators having obtained a remarkable degree of success, with an astoundingly high rate of recovery, and others having found such therapy of no value whatever.[9] No attempt will be made here to review the literature in detail, for the recent reports of Dynes,[10] Wittson [11] and Ripley, Shorr and Papanicolaou [12] have adequately covered this point. Suffice it to say that one finds it extremely difficult to draw any conclusions because of the wide diversity of results and opinions. Rather than to attempt such deductions, it seemed to us more appropriate to look for reasons for this diversity of results.

Several reasons for the remarkable contradiction in results suggest themselves. First, the criteria for the diagnosis of involutional melancholia are not definite and specific, and it is easily understandable that psychiatrists might well disagree on the diagnosis of psychotic states arising in the involutional period. It is well known that there are other psychotic reaction types, similar in many respects to the classic melancholia, which make their appearance at this time. Manic-depressive psychoses not uncommonly appear concurrently with the involution process, and many paranoid conditions, which often have depressive features, frequently become manifest at this age. Occasionally schizophrenia does not develop until the fourth or fifth decade of life.

Another factor which may be considered responsible for the variable results is the choice of the dose of estrogen. Some investigators have

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9. Werner, A. A.; Johns, G.; Hoctor, E.; Ault, C. C.; Kohler, L., and Weis, M.: Involutional Melancholia: Probable Etiology and Treatment, J. A. M. A. **103**:13 (July 7) 1934. Ault, C. C.; Hoctor, E., and Werner, A. A.: Theelin Therapy in the Psychoses, ibid. **109**:1786 (Nov. 27) 1937. Little, G. A., and Cameron, D. E.: Effects of Theelin on Anxiety, Canad. M. A. J. **37**:144 (Aug.) 1937. Schube, P. G.; McManamy, M. G.; Frapp, C. E., and Houser, G. F.: Involutional Melancholia: Treatment with Theelin, Arch. Neurol. & Psychiat. **28**: 505 (Sept.) 1937. Notkin, J.; Dennes, B., and Huddart, V.: Folliculin Menformon (Theelin) Treatment of Involutional Melancholia, Psychiatric Quart. **14**:157 (Jan.) 1940.

10. Dynes, J. B.: Estrogenic Therapy of Involutional Melancholia, Arch. Neurol. & Psychiat. **42**:248 (Aug.) 1939.

11. Wittson, C. L.: Involutional Melancholia, Psychiatric Quart. **14**:167 (Jan.) 1940.

12. Ripley, H. S.; Shorr, E., and Papanicolaou, G. N.: The Effect of Treatment of Depression in the Menopause with Estrogenic Hormone, Am. J. Psychiat. **96**:905 (Jan.) 1940.

used such small doses that one would be surprised if any remarkable results were obtained. At the other extreme, enormous quantities of estrogen seemingly were ineffective in the cases of Ripley and his associates.[12] Furthermore, there may be a great difference in the interpretation of the results obtained. Undoubtedly some investigators feel that nothing less than absolute return to normality is necessary before good results can be said to have been obtained. Again, others are inclined to consider any slight change in the patient's condition as evidence of definite improvement. It would appear, then, that the proper evaluation of this controversial subject would require a detailed individual analysis of every case in which treatment with estrogen was employed, even though this would involve a bulky, and perhaps cumbersome, literature.

METHOD

Twenty-four women were selected at random from a group exhibiting depressive psychoses associated with or following the menopause. They were given thorough physical, including pelvic, examinations, and the laboratory studies included complete blood counts, sugar tolerance tests and determinations of the cholesterol content of the blood, the basal metabolic rate (when possible) and the urinary excretion of gonadotropin. The response to treatment was followed in nearly all cases by examination of the vaginal smear. A deliberate effort was made to retain exactly the same therapeutic and environmental conditions which existed prior to treatment. Half of the patients were given estrogen in the form of estrone (theelin); the other half received androgen in the form of testosterone. The dosage was established at a level intermediate between the high and the low values reported by other investigators. The patients treated with estrone received 1 mg. three times a week until at least 20 mg. was given. The other group received 35 mg. of testosterone three times a week for one month and then 25 mg. three times a week until a minimum of 800 mg. was given. The total doses and the duration of treatment varied to a large extent with the condition and the response of the patient. In cases in which the patients showed improvement the injections were reduced in quantity and frequency in an effort to "taper off." The reason for giving androgen is strictly endocrinologic and will not be discussed in detail. It seems adequate to refer to the work of Kurzrok and his associates [13] and of others,[14] who have demonstrated the similarity of effects and the parallelism in the therapeutic results of androgen and estrogen in women during the menopause.

RESULTS

Our results are briefly summarized in the accompanying table. The changes in the physiologic status of all patients were definite. In the

13. Kurzrok, L.; Birnberg, D. H., and Livingston, S.: The Treatment of Female Menopause with Male Sex Hormone, Endocrinology **24**:347 (March) 1939.

14. Salmon, U.: Effects of Testosterone Propionate upon Gonadotropic Hormone Excretion and Vaginal Smears of Human Female Castrate, Proc. Soc. Exper. Biol. & Med. **37**:488 (Dec.) 1937. Shorr, E.; Papanicolaou, G. N., and Stimmel, B.: Neutralization of Ovarian Follicular Hormone in Women by Simultaneous Administration of Male Sex Hormone, ibid. **38**:759 (June) 1938.

Data on Results of Treatment of Involutional Melancholia with Androgen and Estrogen

Patient	Age, Yr.	Duration, Months: Meno-pause	Duration, Months: Psy-chosis	Weeks of Treat-ment	Substance Given	Dose, Mg.	Result	Follow-Up Observations
				"Classic" Involutional Melancholia				
M. N.	50	34	36	15	Estrone	50	No improvement	Condition unchanged
H. P.	55	6	4	18	Estrone	65	No improvement	Condition unchanged
F. S.	53	71	3	8	Estrone	38	No improvement	Condition unchanged
A. W.	49	15	12	11	Testosterone	1,060	No improvement	Condition unchanged
M. R.	51	12	11	17	Testosterone	1,520	No improvement	Condition unchanged
H. K.	51	18	6	17	Testosterone	1,360	No improvement	Condition unchanged
H. B.	50	27	26	12	Testosterone	1,185	No improvement	Condition unchanged
E. M.	52	6	1	10	Testosterone	1,250	No improvement	Condition unchanged
M. B.	56	30	24	15 3	Estrone Testosterone	40 225	Moderate improvement	Home 1 year; much improved
C. W.	47	20*	6	11	Estrone	33	No improvement	Home 7 months
Z. A.	55	48	18	18	Testosterone	1,395	Moderate improvement	Home 1 year; recovery
L. B.	42	3*	2	18	Testosterone	1,300	Moderate improvement	Home 10 months; recovery
E. C.	46	24	12	20	Testosterone	1,870	Moderate improvement	Home 11 months; recovery
M. S.	41	48 (cessation ?)	4	11	Estrone	22	Recovery	Excellent health
				"Atypical" Involutional Psychosis				
E. B.	50	4+	5	16	Estrone	51	No improvement	Condition unchanged
O. M.	45	14 (cessation ?)	6	20	Estrone	70	No improvement †	Condition unchanged
L. W.	53	21	18	16	Estrone	51	No improvement	Condition unchanged
V. T.	40	16 (cessation)	9	17 5	Estrone Testosterone	49 500	Moderate improvement	Home 8 months; employed
C. V.	47	12*	12	17	Estrone	50	Moderate improvement	Recovery
B. H.	51	12	9	9	Estrone	27	Recovery ‡	Recovery
I. O.	42	18* (irregular)	16	14	Testosterone	1,030	Recovery	Recovery
G. M.	37	12 ?*	15	14	Testosterone	935	Marked improvement	Recovery
C. H.	47	7*	3	10	Testosterone	810	Marked improvement	Home 18 months §
C. W.	47	70 (roentgen climacteric)	16	14	Testosterone	935	Moderate improvement	Complete relapse

* Regular menstruation was resumed after cessation of treatment, usually several months after last injection.

† Remarkable recovery after one month of treatment; patient was discharged while still on high dosage and then received none at all, was returned to institution within one month in a worse condition than before and failed to respond to further therapy.

‡ Recovery was delayed, beginning about the time treatment stopped.

§ Regular menstruation was resumed two months after last injection and stopped again after six months; hot flashes, etc., returned, but patient has been able to remain at home.

majority there was a considerable gain in weight, averaging 15 pounds (6.8 Kg.). Those who were anemic tended to show a rise toward normal in the red cell count. Slightly more than half of the patients had a decreased dextrose tolerance at the beginning of the therapy, and all of these showed a return or an approximation to normal values. The cholesterol content of the blood was usually high at the beginning and showed an average drop of 15 mg. per hundred cubic centimeters. The basal metabolic rate, in the cases in which it was determined, was somewhat below normal and after therapy rose to within the normal range, except in 1 case in which myxedema developed and thyroid medication was required.

The response shown in the vaginal smear and the excretion of gonadotropin in the urine of these patients have been reported on previously.[15] Briefly, the patients who received estrone presented the usual "follicular" changes in the vaginal smear, while the smears of the group treated with testosterone indicated conversion to or persistence in the atrophic state, depending on the previous condition. Approximately half of the patients had exhibited an abnormally high excretion of gonadotropin prior to therapy. This was reduced to within normal limits in all but 1 case.

An unexpected effect was the reappearance of regular menstruation in a fairly large number of our patients. This did not constitute the simple estrogen withdrawal bleeding but represented a regular cyclic menstruation. It may be of significance that return of menstrual function occurred only in patients showing psychiatric improvement. Of the 6 patients who had such a return of menstruation, 5 are still having monthly periods, more than a year after discontinuance of treatment. The other patient had eight regular periods, which were followed by typical menopausal symptoms. Another patient, who had had roentgen castration six years before and had ceased to menstruate, began to bleed one and a half months after cessation of testosterone therapy. This bleeding lasted five days, when a curettage was done and the endometrium was found to be in a hyperplastic or excessively proliferative state. The patient has had no subsequent bleeding in the past fifteen months of observation.

Psychiatrically, some measure of benefit from the therapy was observed in 12 of the 24 patients, or 50 per cent. The criterion of improvement in these patients was considered to be the ability to return home and carry on fairly well in their own environment. Some of

15. Rothermich, N. O.: A Comparative Study of the Effects of Male and Female Sex Hormones on the Human Vaginal Smear, Endocrinology **25**:520 (Oct.) 1939. Rothermich, N. O., and Foltz, L. M.: A Comparative Study of the Effects of Male and Female Sex Hormones on the Pituitary Gonadotropic Function in Women, ibid. **27**:37 (July) 1940.

the patients whose condition was designated as unimproved showed various degrees of lessening of their agitation and depression but were unanimously considered unable to return to their homes, and hence were said to have shown no significant improvement.

A critical analysis of each case was undertaken by one of us without previous knowledge of the kind of treatment or its effects. This resulted in the division of the patients into two groups. Fourteen patients presented the classic, or textbook, picture of involutional melancholia, which is too well known to need further elaboration. The remaining 10 patients exhibited many atypical features, such as exaggerated paranoid trends, cyclothymic coloring, psychoneurotic tendencies and schizoid patterns. Another important difference was the absence of "rigidity" features in the prepsychotic personality of these patients; this might well be a necessary criterion, without which the diagnosis of classic melancholia is untenable. All patients of this group, while exhibiting psychotic depression associated with the menopause, undoubtedly showed "tainted," or atypical, features to such a degree that no true psychiatric classification was possible.

Examination of the clinical results after this categoric separation reveals a remarkable difference. In the group with "classic" melancholia, only 5 of the 14 patients could be considered as benefited, which reduces the percentage of improvement to about 35 per cent. Since spontaneous recovery in this condition is generally considered to be slightly higher than 25 per cent, our results can hardly be considered therapeutically significant. In the other, or "atypical," group, 7 of the 10 patients, or 70 per cent, showed clinical improvement or recovery. Follow-up studies of the patients, carried out for as long as eighteen months, bore out the consistency of our results in all but 2 cases. One patient had been home only two months when she suffered a complete relapse and was returned to the institution. One other patient who received estrone and was considered by us as unimproved later made a remarkable recovery and has been at home for five months. While it is possible that this patient may have been benefited by the endocrine therapy, we feel that the latent period in improvement prohibits her inclusion in the list of those who showed improvement.

Of the 12 patients who showed improvement, 7 received testosterone; of the atypical group of 7 who improved, 4 were treated with testosterone and 3 with estrone. Briefly, it may be said that androgen and estrogen are equally effective in treatment of psychoses associated with the menopause.

COMMENT

From the results obtained by us, it is apparent that endocrine therapy directed at the depression of pituitary function is of little or no avail in the treatment of classic forms of involutional melancholia. Such

a poor therapeutic response suggests that endocrine derangement is not an important etiologic factor in this disease.

Patients exhibiting psychoses similar in many respects to involutional melancholia but with "tainted," or atypical, features showed a remarkably good response to such therapy. The mere fact that they required institutionalization (in some cases for long periods) indicates that their condition transcended the simple menopause syndrome. This distinction has recently been pointed out by Ripley, Shorr and Papanicolaou,[12] although they seemingly did not emphasize the possible overlapping in diagnostic criteria. If we consider the therapeutic response as a point of argument with regard to the etiologic factors, we are forced to admit that in a certain few instances the endocrine imbalance occurring in the climacteric, or menopausal, state is capable of producing a psychosis. However, the manifestations of such a psychosis are extremely varied, although they are essentially dissimilar to the classic picture of involutional melancholia. In ordinary institutional routine, however, those conditions to which we have applied the term "atypical" might well be diagnosed arbitrarily as involutional melancholia, for practically all patients with such states exhibited depression occurring in the involution period. The finer distinction depends primarily on the absence of the typical history of "rigidity" in personality and on various deviations from the classic melancholia in the psychotic pattern which we have emphasized. Because of the remarkable difference in response to estrogen therapy of our patients with typical and with atypical involutional psychoses, we are of the opinion that our results may offer an explanation of the differences obtained by the various groups of investigators.

SUMMARY

Twenty-four patients exhibiting depressive psychoses associated with or following the menopause were given large quantities of estrogen and androgen. The patients were divided into two groups the first, of which, consisting of 14, presented the classic picture of involutional melancholia, while the remaining 10 had an involutional psychosis with atypical features. In the group with true melancholia the rate of improvement was but little greater than that which usually occurs spontaneously. However, 70 per cent of the other, or atypical, group of patients improved to the extent of being able to return home and carry on a fairly normal social existence. Further, laboratory data indicated that treatment with estrogen and androgen produced basic physiologic alterations in nearly all of the patients, regardless of the psychiatric result.

CONCLUSION

Endocrine therapy of the condition described as classic involutional melancholia is of doubtful value. Women in whom atypical depressive

psychoses develop during or after the onset of the menopause may show a remarkable degree of improvement under treatment with estrogen and androgen.

REPORT OF CASES

Inasmuch as this field of investigation is in such a controversial state, we feel it advisable to record a brief history and psychiatric analysis of each patient treated.

CASE 1.—M. N., aged 50, married, a high school graduate, was said throughout life to have been restricted in her social activity, very religious, meticulous and orderly, devoid of humor and lacking in sexual drive. She began to have periods of depression late in 1935. At the time of admission to the hospital, in May 1936, her menstrual periods were infrequent and stopped entirely soon after. She gradually became more depressed, and self-accusatory trends developed. She had hypochondriacal delusions, felt that treatment was utterly hopeless and showed considerable anxiety and agitation.

The diagnosis was involutional melancholia.

In September 1938 treatment with estrone (theelin) was begun. She received a total of 500,000 international units over a period of twenty weeks. In March 1929 she had shown no change whatever, and one year later her condition was unimproved.

CASE 2.—H. P., aged 55, a widow, with 3 adult children, had had irregular menses for some time, and menstruation finally stopped entirely in April 1938. She was said to have been nervous and to have had "blue" spells for several years, especially since the death of her husband, in 1935. Throughout her life she was said to have been energetic, capable and determined, to have been a "good" woman and never to have deviated from a fixed path. On admission, in August 1938, she showed extreme agitation, anxiety and depression. She was constantly fearful of impending catastrophe.

The diagnosis was involutional melancholia.

She received a total of 650,000 international units of estrone over a period of eighteen weeks but failed to show any response whatever and has remained in the same condition ever since.

The result was no improvement.

CASE 3.—F. S., aged 53, was married but had no children. The menopause occurred five years prior to admission. She was said to have been well adjusted socially but to have had a rigid type of personality. Her psychosis began early in 1938 and showed the typical acute anxiety and agitated depression of involutional melancholia. She believed that she and all her family were condemned because of her autoerotic practices in the past. She made several suicidal attempts.

The diagnosis was involutional melancholia.

She received a total of 380,000 international units of estrone over a period of eleven weeks but failed to show any change and has remained in the same condition.

The result was no improvement.

CASE 4.—A. W., aged 49, a single woman, had always lived with her parents on a farm and had had a very restricted and sheltered life. The menses ceased entirely in September 1937, and severe vasomotor symptoms had been present for

one year. The mental picture was that of typical melancholia, with severe agitated depression, utter hopelessness regarding her own future and suicidal trends.

The diagnosis was involutional melancholia.

She was given 1,060 mg. of testosterone in fourteen weeks. She showed some physical improvement, with a marked gain in weight, but there was no change in her mental condition.

The result was no improvement.

CASE 5.—M. R., aged 51, was born in Germany and came to this country in 1930. The sister stated that the patient's marriage was not satisfactory, although the patient denied this. The menopause occurred in September 1937, and the psychosis began one month later. While in the institution she was restless and agitated and had the persistent delusions that she never slept, that she was cursed and possessed by the devil and that she would never get well.

The diagnosis was involutional melancholia.

She was given a total of 1,520 mg. of testosterone in a period of twenty weeks. During this time her agitation subsided considerably, although her attitude toward her future and her delusions of possession by the devil remained. However, at no time was she able to leave the institution and hence was considered unimproved. Her condition has remained unchanged since.

The result was no improvement.

CASE 6.—H. K., aged 51, single, lived with her parents and a maiden sister on a farm and had a very restricted, narrow life. The parents died about six years before the patient's admission to the hospital. Menstruation became irregular and finally ceased entirely in April 1937. She gradually became depressed and worried about her financial security. A suicidal attempt, which was nearly successful, precipitated her admission to the hospital, in April 1938. Since admission she has been restless and frequently threatened suicide. She expressed many somatic delusions and a completely hopeless, despairing attitude.

The diagnosis was involutional melancholia.

She was given a total of 1,360 mg. of testosterone over a period of sixteen weeks. However, she failed to show any change and has remained in the same condition since.

The result was no improvement.

CASE 7.—H. B., aged 50, was married and had an adult son. She graduated from high school and had a business school training, after which she worked in an office. She was considered capable and intelligent. At the age of 23 she married a farmer who was considered beneath her intellectually. She was always a hard worker, never mixed much in society and followed a rather strict mode of living. She had had irregular menses and vasomotor disturbances for several years, with complete menopause two months before her admission to the institution in September 1936. She presented a picture of marked anxiety and agitated depression with self-accusatory trends. She said that she had committed the unpardonable sin, that she was the cause of all the sin and crimes in the world and that everybody has to die because of her.

The diagnosis was involutional melancholia.

She was given a total of 1,185 mg. of testosterone over a period of seventeen weeks but failed to show any change whatever.

The result was no improvement.

CASE 8.—E. M., aged 52, a widow, had a common school education and had worked in a restaurant and factory prior to her marriage, at the age of 41. She

was always considered a "good" girl, a hard worker and very religious. She was admitted to the institution in October 1938. Her husband had died eleven months before, and after his death she cried continuously, refused to eat and finally became extremely agitated. At the time of admission she was resistive and expressed delusions of self-accusatory and nihilistic nature. Her menstrual history could not be obtained, but she has had no periods since entering the hospital.

The diagnosis was involutional melancholia.

She was given 1,250 mg. of testosterone over a period of two months, but her condition remained unchanged.

The result was no improvement.

CASE 9.—M. B., aged 56, married, with 3 children, had had the typical "rigid" personality of melancholia all her life. The menopause had occurred some time before 1936, and she had had vasomotor symptoms since. She was admitted to the institution in July 1937 with a history of mental illness for nine months. She was very resistive, restless and agitated and had delusions of being lost and of being sent to the electric chair. She imagined that her family was being burned because of her misdeeds. She required tube feeding much of the time.

The diagnosis was involutional melancholia.

She was given 400,000 international units of estrone and 200 mg. of testosterone over a period of five months.

Her agitation subsided; she began to eat voluntarily and was much more cooperative. Her delusional ideas began to fade, although they were still present at the time she was taken home. A year later she was still at home and apparently in good condition. Her family reports that she is doing well and no longer expresses delusions. She was considered much improved.

CASE 10.—C. W., aged 47, single, is the sister of the patient in case 4, and there are many characteristics of folie à deux in the two cases. She resided on a farm and, like her sister, lived a very narrow life. Symptoms developed shortly after her sister was admitted to the institution. She herself was admitted two months later. The menopause had occurred one and a half years previously. Both sisters were strongly attached to the father, and their illness developed shortly after his death. On admission this patient, the younger of the two, showed great restlessness, depression and marked anxiety. She expressed a feeling of utter hopelessness for the future and fear that she would be left alone to starve. She always expressed great concern regarding her sister.

The diagnosis was involutional melancholia.

She was given a total of 330,000 international units of estrone over a period of eleven weeks, but her condition was unchanged at that time and remained so for several months. However, she later began to improve and was finally permitted to go home. A check-up after she had been at home for seven months revealed that she was still in good condition, and the family reported that she was adjusting well socially. In this case improvement was not due to endocrine therapy.

CASE 11.—Z. A., aged 55, married, with 2 children, was said to have always been rather sickly, nervous and puritanical and to have exhibited the typical "rigid" personality of melancholia. Her menopause had occurred some three years before admission to the hospital, in October 1937. Her mental illness came on gradually over a period of two years. She became more depressed and agitated, showed self-accusatory delusions and had a hopeless attitude regarding her future. She was fed by tube much of the time prior to institution of therapy.

The diagnosis was involutional melancholia. She was given a total of 1,395 mg. of testosterone over a period of five months and showed marked improvement. She left the hospital shortly after therapy was discontinued and has remained at home ever since. She has adjusted herself well and takes care of her household duties thoroughly.

The result was marked improvement.

CASE 12.—L. B., aged 42, married, with 4 children, was said to have had an unhappy childhood, but had worked her way through high school and teachers' college. She taught school before her marriage, at the age of 21. Her marriage was fairly congenial until twelve years ago, when her husband had epidemic encephalitis. Since that time his partial invalidism and inability to work, in addition to his changes in personality, had made him difficult to live with. In later years the behavior of her two daughters gave her serious cause for worry. Menstruation had been irregular for about one year and finally ceased in June 1938. Her mental disturbance began in July, and she was admitted to the institution in August 1938. She showed extreme anxiety and agitated depression. She refused to eat and attempted suicide. She feared that her family would starve to death and that she would have to undergo torture.

The diagnosis was involutional melancholia.

She was given a total of 1,300 mg. of testosterone over a period of eighteen weeks. On two occasions she was allowed to go home but failed to continue treatments and had to be returned in a short time. Finally, treatments were carried to completion, and she was then permitted to go home. Regular menstruation reappeared, and one year later she was still home; menstruation was still regular, and her mental and physical conditions were excellent.

The result was recovery.

CASE 13.—E. C., aged 46, was a widow, with 2 children. Her mother had suffered from mental illness during the menopause but later recovered. Throughout her life the patient had had a very "rigid" personality. The menopause began in 1936 and mental symptoms a year later. She gradually became more depressed, and on admission to the hospital, in March 1938, she showed extreme anxiety, agitated depression, self-accusatory delusions and fears of impending harm. She believed that she had a devil inside her and that she was doomed to the penitentiary. She refused to eat and moaned and cried continuously. She had shown slight improvement when endocrine therapy was begun.

The diagnosis was involutional melancholia.

She was given a total of 1,870 mg. of testosterone over a period of twenty weeks and showed a remarkable return of physical health. She gradually and progressively improved mentally and left the hospital a short time afterward. A year later she was still at home and carrying on her social and household duties well.

The result was marked improvement.

CASE 14.—M. S., aged 41, married, with 3 children, had had a common school education and worked in a factory before her marriage, at the age of 21. She was introvertive, extremely religious, completely lacking in sexual drive and very meticulous and orderly; of all the patients, indeed, she presented the most classic "rigidity" of personality. She had had a pelvic operation in 1935, but it could not be ascertained whether the ovaries were removed. Mental illness began in March 1938, and she was admitted to the hospital in August of the same year.

She had attempted suicide. She presented a picture of anxiety and depression and expressed the belief that she had committed some grave sin.

The diagnosis was involutional melancholia. She was given 125,000 international units of estrone and showed remarkable improvement. She was allowed to go home and continued to receive estrogen in gradually decreasing doses. Therapy was discontinued after eleven weeks, when she had received a total of 219,000 international units. One year later she was said to be in excellent health.

The result was recovery.

CASE 15.—E. B., aged 50, married, with no children, had been somewhat introvertive and sensitive. For some time she had seemed dissatisfied, worried and suspicious of people; acute mental symptoms began in the spring of 1938, and she was admitted to the hospital in June 1938. No history of the menopause could be obtained, but she had had no periods since admission to the hospital. Her mental picture was that of depression, although she showed extreme irritability and was uncooperative. She had strong persecutory delusions, and because of this she was disagreeable and failed to get along with the other patients. She did not believe that anything was wrong with her and refused to take any treatment.

The diagnosis was paranoid involutional psychosis; other possibilities included paranoid condition, or even paranoid schizophrenia.

She was given 510,000 international units of estrone over a period of sixteen weeks but failed to show any change whatever.

The result was no improvement.

CASE 16.—O. M., aged 45, was divorced and had no children. She was a college graduate and had held a number of responsible positions, although she frequently changed from one to another because she felt she was overworked or was unduly nervous. She was strongly introvertive and showed little interest in the opposite sex. She had never had a definite mental illness until the present one, but she had had several "nervous breakdowns" following critical events in her life. She had a pelvic operation in July 1937, with removal of the uterus, but whether this included the ovaries is not known. In November 1937 she was married to an elderly man but left him after one week because of her revulsion toward sexual relations. She explained that she had married him only because of a feeling of insecurity on her part and uncertainty of the future. Furthermore, she gave a long history of various somatic symptoms and frequently consulted physicians for these ailments. Signs of acute mental disturbance began in February 1938 with persecutory delusions and ideas of reference, such as a feeling that people were following her. She became depressed and agitated and was admitted to the hospital in March 1938. Prior to therapy she had shown great restlessness and agitation, was always fearful that she would be involved in some political scandal and felt that she had done something wrong for which she should make amends. She refused to be employed, paced the floor constantly and took no pride in her appearance.

The diagnosis was atypical involutional or menopausal psychosis; true involutional melancholia was a possibility, but there was a strong schizoid coloring, together with certain cyclothymic features. There was also some support for a diagnosis of psychoneurosis.

She was given 120,000 international units of estrone and made a remarkable recovery. However, she was removed from the institution while still on a very high dosage and received no treatment whatever while at home. She broke down again and was readmitted within a month in a worse condition than before. Estrone

therapy was resumed, until she had received a total of 700,000 international units. However, she failed to show any change, and a year later was in the same condition.

The result was no improvement.

CASE 17.—L. W., aged 53, a widow, with 2 adult children, was intelligent, capable and sociable. Her husband, who had been a successful attorney, died in 1935, and it was then discovered that they had been living beyond their income and that debts consumed most of his estate. The patient worried considerably, and extreme depression finally precipitated her admission to the hospital, in September 1937. The menopause had begun late in 1936. At the time of her admission she was retarded, answered questions only in monosyllables, if at all, and showed extreme depression. Forced feeding and occasionally tube feeding had to be resorted to, and psychomotor activity had almost disappeared. However, she had the delusion that she must go to the penitentiary and that her stomach and bowels were not functioning. There was little evidence of anxiety and no agitation.

The diagnosis was atypical involutional or menopausal psychosis; there were many features to suggest a depressed state of manic-depressive psychosis.

The patient received a total of 510,000 international units of estrone over a period of sixteen weeks but failed to show any change whatever.

The result was no improvement.

CASE 18.—V. T., aged 40, divorced, with 2 sons, had had a common school education and had worked most of her life in a glass factory. She apparently was well adjusted socially, had shown a normal interest in the opposite sex and had a rather broad outlook on life. Her husband was abusive and insisted on being divorced from her, to which she consented late in 1936. However, because of her love for him, she was extremely upset by this turn of events. She had a hysterectomy in August 1937 which included removal of the ovaries, and about three months later she began to show mental disturbances. At first this varied from mutism to agitation and depression. She threatened suicide and said that her husband had "framed" her to kill some one. She was fearful that she had killed her children and her mother. She had auditory hallucinations and many delusions. She misidentified persons and thought the radio broadcast lies about her.

The diagnosis was atypical involution or menopausal psychosis. A perplexed type of manic-depressive psychosis may well be considered, and there were certain features suggesting catatonic schizophrenia.

She received 490,000 international units of estrone, followed by 500 mg. of testosterone, over a period of twenty-two weeks. She improved to the extent that she was able to leave the hospital in the care of relatives. Her improvement continued, and she finally returned to work and has remained in employment since.

The result was marked improvement.

CASE 19.—C. V., aged 47, married, with 1 grown son, was apparently well adjusted socially but throughout her life had had numerous physical ailments and frequently consulted physicians. Her menstrual cycles became irregular in 1937 and finally ceased entirely in September of that year. A month later she took excessive quantities of sedatives and exhibited what appeared to be a drug psychosis; on recovery from this she showed extreme depression. She was admitted to a private sanatorium in January 1938 and was transferred to the Columbus State Hospital in March. At the time of admission she was agitated and depressed and expressed self-accusatory delusions. However, true affective depression appeared to be lacking, and there were expressions of other bizarre delusions. The agitation alternated with periods of psychomotor retardation and

mutism. Until the time of estrogen therapy she had shown no change whatever and had frequently expressed the idea that she was already dead and in hell.

The diagnosis was atypical involutional or menopausal psychosis; also to be considered are the mixed and perplexed types of manic-depressive psychosis and the possibility of schizophrenia.

She received a total of 500,000 international units of estrone over a period of seventeen weeks and showed considerable improvement. Her emotional state was much better. She frequently smiled and laughed at the absurdity of other patients' delusions and was cooperative. At this time, through a misunderstanding, she received a short course of metrazol therapy and then was allowed to leave the hospital in the care of relatives. One year later she was reported to be in very good condition and to be taking care of her household and performing her social duties normally. She had had a return of menstrual function, with regular periods.

The result was recovery.

Case 20.—B. H., aged 51, was married and had 8 children. Her first husband, by whom she had had all her children, died in 1928. He had been alcoholic and abusive, and this necessitated her working hard to keep her family together. She took in washing and did a maid's work by day and various odd jobs until she was remarried in 1936. The second marriage was congenial, and she seemed to be getting along well. The menopause began in September 1937. In November mental illness began rather abruptly. She attended revival meetings, claimed to have been converted and showed acute religious mania. She was admitted to the institution in December 1937, and at that time her illness was characterized by irresponsible behavior, consisting of pronounced delusions, mostly of a religious persecutory type, visual and auditory hallucinations and marked irritability. There was also considerable depression. She remained essentially in this state until therapy was begun.

The diagnosis was atypical involutional or menopausal psychosis; the staff diagnosis was that of the paranoid type of involutional melancholia, but the many atypical features in the case eliminated it from those of "classic melancholia."

She received 270,000 international units of estrone over a period of nine weeks. She did not show any change until the last week of therapy, when she began to improve. This continued, and within three months she was able to leave the hospital, entirely well. One year later she was reported to be completely recovered.

The result was recovery.

Case 21.—I. O., aged 42, married, with 4 children, had had a common school education, after which she worked in a shoe factory until her marriage, at the age of 18. After the birth of her fourth child she was delirious for a few months and did not walk for four years. The exact nature of this condition could not be determined, although it left her slightly ataxic, with hyperactive tendon reflexes of the lower extremities. Menstruation became irregular in the spring of 1937, and at that time she began to show depression. On admission to the hospital in June 1937 she was restless, agitated and depressed. She talked about not wanting to live because of the wicked things she had done. She claimed to have had extramarital sexual relations, although her husband did not believe this. She was constantly afraid of being sent to jail. Her condition had remained essentially unchanged up to the time of beginning of therapy.

The diagnosis was atypical involutional or menopausal psychosis; there are many aspects to suggest an anxiety psychoneurosis.

She received 1,030 mg. of testosterone over a period of fourteen weeks and showed progressive improvement. During the therapy evidence of impending myxedema developed, and thyroid medication was required. She was allowed to leave the hospital in December 1939 and adjusted herself well to a comparatively adverse environment. Her menstrual periods resumed two months after cessation of therapy and have remained regular ever since.

The result was recovery.

CASE 22.—G. M., aged 37, was married and had 1 son. After graduation from high school she was married, when she was 19 years of age. She was ambitious and worked hard at home and elsewhere. Her mental illness began six weeks before her admission to the hospital, in June 1937. At about the same time menstruation became irregular. In the early months of her illness she was acutely disturbed, insisting that the hospital was a penitentiary and that she had a venereal disease. She had definite persecutory delusions and hallucinations. She had a slight remission for a short period late in 1937 but was returned to the hospital in January 1938. Since that time her mental symptoms have been marked by hypochondriacal trends.

The diagnosis was atypical involutional or menopausal psychosis; there were many features to suggest a simple paranoid condition, although such a diagnosis would obviously be inadequate. She was given 935 mg. of testosterone over a period of fourteen weeks and showed progressive improvement. A short time later she was allowed to leave the hospital and adjusted herself well to adverse conditions. Her husband, who had been living with another woman, insisted on a divorce, which she finally gave him. She found employment and has worked at a gainful occupation ever since.

The result was recovery.

CASE 23.—C. H., aged 47, single, had held responsible positions in two insurance offices for twenty-six years, having been discharged from the second position because of "economy measures." She became nervous and worried and was discouraged by her inability to find employment. She expressed a feeling of insecurity and fear of the future. A suicidal attempt, which was nearly successful, was responsible for her hospitalization. While in the hospital she was nervous and worried but showed no remarkable agitation. She was hypochondriacal and had numerous physical complaints. Her previous history had shown a rather good adjustment to life, with normal attraction to the opposite sex; she had used alcohol for years and in increasing amounts since her unemployment. The menopause had occurred in January 1938, six months prior to her admission to the hospital, and this was followed by numerous vasomotor symptoms.

The diagnosis was atypical involutional or menopausal psychosis; the condition of this patient could well be placed in the category of anxiety psychoneuroses.

She received a total of 810 mg. of testosterone over a period of ten weeks. She improved rapidly and was allowed to leave the hospital a short time after the institution of therapy. While at home she continued to receive androgen therapy in gradually decreasing doses. Two months after cessation of treatment regular menstrual cycles reappeared. She was returned to the institution in March 1939 because of a reported suicidal threat. However, the report could not be substantiated, and she appeared to be in good condition; she was allowed to leave again in a few days. A check-up later revealed that she was still socially adjusted at home. Her menses had again ceased some time in the summer of 1939, and this was followed by vasomotor symptoms of a lesser degree.

The result was marked improvement.

CASE 24.—C. W., aged 49, was married and had no children. She had an excellent cultural background and had received a college education, but married beneath her social level. Because of this marriage her wealthy foster father disinherited her. Nevertheless, her marriage appeared to have been congenial. In 1932 she was given roentgen ray therapy over the ovaries for excessive menstruation. A short time after this the menses stopped altogether, and a classic acromegalic syndrome began to develop. However, no mental symptoms appeared until two years prior to her admission to the hospital, and then very gradually. She had some paranoid delusions and visual hallucinations. The latter consisted mostly of seeing colored lights and searchlights at night. In addition, she showed muscular weakness, headaches and moderate contraction of the visual fields. There was some element of depression, although this was rather mild.

There is admittedly considerable difficulty in classifying this case; the diagnosis of psychosis associated with endocrine disturbances is acceptable, but not helpful. The most likely condition is a pituitary tumor. However, even this diagnosis will admit the classification of postcastration or menopausal psychosis. The patient received 935 mg. of testosterone at irregular intervals over a period of fourteen weeks. A short time after institution of therapy she improved remarkably and was allowed to go home. Ten days later she returned in relapse and androgen therapy was resumed. Again, improvement occurred and she was once more permitted to return home. No definite arrangements could be made for continuing therapy at home, and consequently relapse again occurred. About this time vaginal bleeding appeared and continued for five days, when an endometrial curettage was done. The endometrium was found to be in a hyperplastic or excessive proliferative stage. Since that time the patient has remained in the institution in a fairly good condition, and no further bleeding has occurred.

The result was moderate improvement. It was felt that this patient could have remained at home if continuation of endocrine therapy had been possible, and hence the result should be considered as favorable.

DILANTIN SODIUM POISONING

REPORT OF A CASE WITH DERMATITIS EXFOLIATIVA, PYREXIA AND HEPATIC AND SPLENIC ENLARGEMENT

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Dilantin sodium is being increasingly used in treatment of epilepsy because it appears to be effective in controlling seizures of the grand mal type in many of the patients who are not benefited by phenobarbital and bromides. The occurrence of hepatomegaly and splenomegaly in association with pyrexia, a severe scarlatiniform erythema and widespread dermatitis eventuating in dermatitis exfoliativa in a case in which a large amount of the drug had been taken warrants a report.

REPORT OF CASE

History.—Mrs. S. S., aged 34, white, was admitted to the Jewish Hospital on June 7, 1940, complaining of weakness, fever and a rash of four days' duration. Her family history was without significance; there had never been a case of epilepsy. Except for the usual sicknesses of childhood, she had never been ill. There had been 3 pregnancies. One child died of pneumonia, and 2 were alive and well.

Epilepsy first appeared in 1936, a few months after the birth of her last child. The attacks were typical of the grand mal type and were usually preceded by peculiar sensations in the epigastrium. At first the seizures occurred three or four times a year. They had become much more frequent in the last year and a half, as many as three attacks a week having occurred.

The patient was examined two months before her admission to the hospital. At that time there were no pathologic findings, the results of neurologic examination was entirely normal and the liver and spleen were not palpable. Phenobarbital and bromides in various doses proved of no value in checking the attacks. On May 7, 1940 she was given dilantin sodium in capsules of 1½ grains (0.097 Gm.) each. A capsule was taken twice daily for the first three days and three times a day thereafter. For the first time in months no epileptic seizure occurred.

On May 21, 1940, after having taken 39 capsules (58½ grains [3.8 Gm.]), she noted a faint rash on her body. It disappeared the following day. By June 3 she had taken 76 capsules (114 grains [7.41 Gm.]). On that day she complained of weakness, headache and a feeling of "burning all over." A rash resembling measles was noted on the face, neck and chest. The eruption extended to the abdomen the next day. On the third day it covered the entire body and intense pruritus set in. The temperature was elevated from the onset, and reached 105 F. the day before she entered the hospital.

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Examination.—On admission to the hospital on June 7, the fourth day of her illness, the patient appeared acutely ill. Slight cyanosis of the lips and finger tips was noted. The temperature was 102 F. The skin of the entire body was the seat of an intense erythema, more marked on the face and chest. The rash on the abdomen and extremities was patchy and consisted of macules and papules which showed a tendency to become confluent. The face showed slight edema. The liver was palpable 2 cm. below the costal border and was tender. The spleen was felt just below the costal margin. The lymph glands were not enlarged. The scleras were not icteric.

Course.—The dermatitis became more intense. The entire surface of the skin was covered with a diffuse scarlatiniform erythema. The face and hands were markedly swollen and edematous. Desquamation began on June 8. It was first observed on the face and hands, and within a few days it became generalized. The liver and spleen continued to enlarge. On the fourth day following admission, the liver extended to 7 cm. below the costal margin and was firm and slightly tender, and the spleen, which was felt 5 cm. below the costal arch, was likewise firm but not tender. The fever gradually subsided, the temperature becoming normal on June 15, the twelfth day of her illness. The dermatitis gradually subsided, and the desquamation continued until complete. Twelve days after the onset of her illness the skin appeared normal. The liver and spleen had progressively decreased in size but were still palpable on the fifteenth day of her illness, the liver being 4 cm. and the spleen 2 cm. below the costal margin.

On June 20, seventeen days after the onset of her illness, a recrudescence occurred. A maculopapular eruption appeared over the extremities and abdomen; the temperature rose sharply to 103 F., and the liver and spleen again enlarged to the maximum size noted at the height of the initial course of her illness. The liver was slightly tender. The temperature subsided after three days; the rash faded without desquamation, and the liver and spleen became smaller. On the day of her discharge (July 6), the liver was felt 2.5 cm. below the costal arch and the spleen was palpable just at the costal margin.

Laboratory Data.—On admission examination of the blood showed no anemia; the leukocytes numbered 10,000 per cubic millimeter, of which 58 per cent were polymorphonuclear neutrophils, 36 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. Subsequent counts showed no essential changes except for a reduction in the leukocyte count. At no time was there eosinophilia. Determinations of the chemical constituents of the blood revealed normal values for sugar, urea nitrogen, uric acid, cholesterol, cholesterol esters and calcium and phosphorus. The icterus index on June 10 was 6.7; on June 14, 6.2 and on June 24, 7.5. The serum phosphatase value was found to be increased; on June 10 it was 15.4 units per hundred cubic centimeters of blood, and a week later it was 11.1 units. A few days before her discharge from the hospital it was found to be normal (5.2 units per hundred cubic centimeters of blood). Examination of the urine showed nothing abnormal. The urobilinogen content was 0.17 mg. per hundred cubic centimeters. A galactose tolerance test, done on July 5, showed an excretion in the urine of 1.92 Gm. in five hours (according to the method of Shay and his associates[1]).

1. Shay, H.; Schloss, E. M., and Rodis, I.: II. The Galactose Tolerance Test in the Differential Diagnosis of Jaundice, Arch. Int. Med. **47**:650 (April) 1931. Studies of bone marrow smears obtained by sternal puncture were made by Dr. Maurice Morrison; the myelograms were entirely normal.

Subsequent Course.—Since her discharge from the hospital, the patient has been taking phenobarbital in ½ grain (0.032 Gm.) doses three times daily. There has been a recurrence of the epileptic seizures. On July 15 the spleen could not be felt; the edge of the liver was palpated 2 cm. below the costal margin. The icterus index determined on July 15 was 4.7.

COMMENT

The toxic effects of dilantin sodium have been reported by Merritt and Putnam,[2] who made the first extensive study of the anticonvulsant properties of the drug, and by several other investigators.[3] The side actions observed are many. The more common are gastrointestinal disturbances, nervous and mental symptoms, hyperplasia of the gums, fever and cutaneous eruptions. Merritt and Putnam [2] observed cutaneous lesions in 5 per cent of their cases. These varied from mild erythema to a diffuse morbilliform eruption. In only 1 of their cases did severe generalized dermatitis with subsequent desquamation develop. In a review of the literature [4] we have been unable to find any other report of hepatomegaly or splenomegaly associated with manifestations of dilantin sodium poisoning.

SUMMARY

A case of dilantin sodium poisoning has been reported. In addition to pyrexia and severe widespread dermatitis that eventuated in dermatitis exfoliativa, marked enlargement of the liver and spleen developed. A recrudescence occurred five days after an apparent recovery.

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2. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in Treatment of Convulsive Seizures: Toxic Symptoms and Their Prevention, Arch. Neurol. & Psychiat. **42**:1053 (Dec.) 1939.

3. Kimball, O. P., and Horan, T. N.: Use of Dilantin in Treatment of Epilepsy, Ann. Int. Med. **13**:787 (Nov.) 1939. Laws, J. J.: Epanutin in Epilepsy, Brit. M. J. **2**:725 (Oct. 7) 1939. Blair, D.; Bailey, K. C., and McGregor, J. S.: Treatment of Epilepsy with Epanutin, Lancet **2**:363 (Aug. 12) 1939. McCartan, W., and Carson, J.: Use of Sodium Diphenyl Hydantoinate, J. Ment. Sc. **85**: 965 (Sept.) 1939. Williams, D.: Treatment of Epilepsy with Sodium Diphenyl Hydantoinate, Lancet **2**:678 (Sept. 23) 1939. Frost, I.: Sodium Diphenyl Hydantoinate in Treatment of Epilepsy: Preliminary Observations in Severe Cases, J. Ment. Sc. **85**:976 (Sept.) 1939. Steel, J. P., and Smith, E. S.: Epanutin in Epilepsy, Lancet **2**:367 (Aug. 12) 1939. Fetterman, J. L.: Dilantin Sodium Therapy in Epilepsy: Report of Study in Progress, J. A. M. A. **114**:396 (Feb. 3) 1940.

4. Merritt and Putnam.[2] Footnote 3.

THE PERIPHERAL NERVES IN CASES OF NUTRITIONAL DEFICIENCY

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CINCINNATI

There are many controversies that afflict the definition of polyneuritis. The most urgent question involves the minimum requirements for the diagnosis. The patient who is suddenly and conspicuously paralyzed in all extremities, who has lost sensation in the distal portions of the limbs and in whom tendon reflexes cannot be obtained does not test diagnostic acumen. But there is confusion at the other extreme. Diagnostic criteria of minimal polyneuritis appear to vary from writer to writer, and some persons disciplined in neurology doubt whether all who seem to speak authoritatively know what polyneuritis is. In fact, neurologists are themselves doubtful in borderline cases. A tendency to include pain in the leg under the heading of polyneuritis might contribute to a therapeutic fashion.

Another controversial point is the nutritional deficiency hypothesis, which is at present rather overworked. No one has advanced any convincing figures to show that the incidence of the paralyzing type of polyneuritis that is usually associated with the ingestion of alcohol is any higher in regions in the southern United States, where nutritional deficiency is more endemic, than in the north. In the nutrition clinic of the Hillman Hospital in Birmingham, Ala., where 2,260 patients with deficiency of nutrition have been observed since February 1938, this type of neuritis rarely is seen unassociated with alcoholism or some severe organic disease. On the other hand, paralytic polyneuritis is not infrequently observed at the Cincinnati General Hospital, where patients

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suffering from nutritional deficiency usually have ingested alcohol in large quantities and over long periods.

In cases of pellagra the incidence of neuritis is high as determined by clinical methods [1] and the incidence of paralyzing polyneuritis (as seen in alcoholism) is practically nil. These facts are significant. In support of the nutritional deficiency hypothesis it has been said that paralytic polyneuritis (associated with alcoholism) represents the final stage of a long-standing process of deficient nutrition. It is said that the nerves have been affected gradually until the process has reached a point where it is no longer reversible, and for recovery to occur the nerve cell must form a new axon. There is no deficiency of nutrition as prolonged as that of the pellagrin in the southern United States, where it is of lifelong duration in some instances. Studies have been made [2] which indicate that the children of pellagrins, and even their dogs, have evidences of pellagra or blacktongue.

Some light might be shed on these problems if there was a reasonably accurate method of determining the presence of neuritis and its severity, besides the usual clinical evaluation, which may not be convincing. If the findings of an accurate laboratory method could be correlated with those of the clinic criteria might be advanced for the diagnosis of minimal polyneuritis. Greenfield and Carmichael [3] have described a method for the histologic study of peripheral nerves. They demonstrated that the myelin sheaths were reduced in number in the nerves of patients with subacute combined degeneration of the spinal cord and that the reduction was of the same type, but not of the same degree, as that found in persons with alcoholic neuritis. We have obtained the best of our morphologic data from the use of the technic described by Greenfield and Carmichael.

METHODS AND RESULTS

For accuracy, it was considered necessary to use nerves from living patients. Specimens of peripheral nerves were obtained from 10 persons with pellagra and from 5 control subjects. The terminal portion of the internal branch of the anterior tibial nerve, which lies between the first and second metatarsal bones, was removed in each case under procaine anesthesia, without pain or disability to the patient. The nerve was carefully dissected away with a minimum of handling, and without crushing or stretching. Usually 3 or 4 cm. was taken and a portion

1. Lewy, F. H.; Spies, T. D., and Aring, C. D.: The Incidence of Neuropathy in Pellagra, Am. J. M. Sc. **199**:840-849, 1940.

2. Spies, T. D.; Walker, A. A., and Woods, A. W.: Pellagra in Infancy and Childhood, J. A. M. A. **113**:1481-1483 (Oct. 14) 1939.

3. Greenfield, J. G., and Carmichael, E. A.: The Peripheral Nerves in Cases of Subacute Combined Degeneration of the Cord, Brain **58**:483-491, 1935.

immediately placed in a brown bottle containing 1 per cent freshly prepared osmic acid. The remainder was placed in dilute solution of formaldehyde U. S. P. (1:10). The portion in osmic acid was then placed in the dark for thirty to thirty-eight hours immediately after removal from the body. The nerves were sectioned in paraffin; those prepared by the osmic acid technic were cut transversely and those fixed in formaldehyde longitudinally. The latter were stained by the Bodian 1 per cent "protargol" (protein silver) method, by the Loyez myelin sheath method and with hematoxylin and eosin. The transverse sections, stained with osmic acid, were cut at 4 to 6 microns, all of the tissue being utilized, and every fifth section was mounted. Then, by elimination, only the sections containing the most myelin sheaths were used for study.

It is difficult to express nutritional deficiency in quantitative terms. There has been an increasing tendency toward the belief that all patients with nutritional deficiency are deficient not only one nutritional element, but several.[4] In the few cases here recorded the indication is that pellagra is without doubt a multiple deficiency. From a careful clinical study, corroborated as far as possible in all instances by chemical studies, the diagnosis of deficiency was arrived at (table).

The thiamine content of the urine excreted during twenty-four hour periods was measured for days before and after the biopsy in all cases. The diagnostic laboratory tests do not reach as far as one would like, but the diagnoses are as accurate as it is possible for them to be at this time. It should be emphasized that they do not rest entirely on clinical acumen.

The majority of the patients who attended the nutrition clinic of the Hillman Hospital complained of pain in the legs. It was uncommon to find neurologic signs in these patients other than tenderness on squeezing the calf muscles and compressing the soles of the feet and some diminution of sensation in the distal portion of the lower extremities. Occasionally the ankle jerks were affected. No selection was exercised in choosing patients for this study, after the plans of the study were formulated. Ten subjects were obtained as they entered the nutrition clinic, after the nature of the procedure had been explained to them. They were ambulatory except for 2 patients (cases 1 and 9). Control material taken from 5 patients at the Cincinnati General Hospital was handled in the same manner as that from the patients with nutritional deficiency. One of the control patients (case 11) was addicted to alcohol.

Since 1 per cent osmic acid stains the normal myelin sheath black, determination of the amount of myelin sheath loss required a count of

4. Aring, C. D., and Spies, T. D.: Vitamin B Deficiency and Nervous Disease, J. Neurol. & Psychiat. **2**:335-360, 1939.

the stained myelin sheaths per square millimeter. The bundle which had been counted was then photographed. A corrected count of the myelin sheaths was then made in the photomicrographs of nerve bundles enlarged 350 diameters. The count was done by the planimetric method, which entailed the use of a transparent celluloid plate ruled into square centimeters. No great difficulty is encountered by this method, which would seem reasonably accurate if care is used to exclude from the planimetric measurements spaces under the perineurium. In the control

Principal Neurologic Findings, Diagnosis and Number of Myelin Sheaths per Square Millimeter of Peripheral Nerve in Ten Cases of Pellagra and in Five Control Cases *

			Neurologic Findings			Diagnosis			Pathologic Changes	
						Deficiency of				
Case No.	Age, Yr.	Sex	Tendon Reflexes	Stocking or Glove Type of Sensory Loss	Vibration	Thiamine	Nicotinic Acid	Riboflavin	Myelin Sheaths, Mean Count	Degeneration of Axis-Cylinders
1	27	F	(AJ) 0	+	±	+++	++	++†	380	++
2	55	F	N	+	N	+	0	0	5,930	ND
3	45	F	N	+	±	++	+	0	6,210	++
4	64	M	N	+	N	+	0	0	2,160	++
5	46	F	N	+	N	+	+	0	4,500	ND
6	59	F	(AJ) ±	+	N	+	±	+	3,900	+
7	27	F	++	+	N	+	++	+	3,491	+
8	62	F	N	Hyperpathia	±	++	+	0	5,155	±
9	56	M	N	0	±	+	±	0	4,780	±
10	28	F	++	Hyperpathia	Hyperpathia	+	++	++‡	2,674	++
11	51	M	N	0	N	Anxiety state; alcoholism; syphilis			5,073	ND
12	36	M	N	0	N	Paranoid schizophrenia			6,542	0
13	22	M	N	0	N	Schizophrenia			6,836	0
14	57	F	N	0	N	Presenile psychosis			7,928	0
15	35	F	N	0	N	Manic-depressive psychosis, depressed phase			8,911	0

* In the table, 0 means absent; AJ, ankle jerk; N, normal; ±, slight or reduced; +, moderate or present; ++, severe or hyperactive, and ND, count not made (insufficient tissue).

† Deficiency in iron

‡ Deficiency in vitamins A and B_6 and iron.

subjects the nerve bundles contained 6,500 to 9,000 myelin sheaths per square millimeter, with the exception of 1 patient (case 11) who was addicted to alcohol. These figures compare favorably with Greenfield and Carmichael's [3] estimation of 5,000 to 10,000 myelin sheaths for the normal nerve. In the patients suffering from nutritional deficiency the nerve bundles rarely contained as many as 5,500 myelin sheaths per square millimeter. Consideration was given to the relationship between the number of myelin sheaths and the age of the patient, and nothing of significance was noted.

To evaluate further the degree of degeneration of the myelin sheaths in these nerves, an estimation was made of the proportion of myelin

sheaths of different sizes in the nerves obtained from the patients with nutritional deficiency as well as in those taken from the controls. Measurement of the diameter of each sheath was made in multiples of 0.6 micron, and the sheaths were tabulated according to size. The proportion of myelin sheaths of each size (ranging from 1.2 to 15 microns) was calculated as a percentage of those in the whole nerve bundle. These percentages were then corrected to the number of myelin sheaths per square millimeter and were taken to represent an approximate estimate of the number at each 0.6 micron of diameter per square millimeter of the cross section of the nerve. The counts were then charted as curves, and the normal nerves were found to contain myelin sheaths ranging from 1 to 11 microns in diameter, with a preponderance of those between 3 and 6 microns (fig. 1 *A*). In cases 2, 3 and 8, in which the peripheral neuritis was the mildest according to histologic study, the curves approximated the normal as far as the smaller sheaths were concerned, with a distinct reduction in the number of the large sheaths (fig. 1 *B*). In cases in which the peripheral neuritis was morphologically of moderate severity (cases 5, 6, 7 and 9) and of the greatest severity (cases 1, 4 and 10), the number of sheaths was distributed according to size (fig. 1 *C* and *D*) in a comparatively even manner along the curve. There were a number of large myelin sheaths measuring up to 15 microns in the nerves from the patients with moderate and severe neuritis. In the nerves from the controls it was rare to find myelin sheaths of 12 microns, and a sheath with a diameter of 10.6 microns was the largest in the nerves of 3 of the 5 subjects.

COMMENT

The peculiarities of size and the reduction of myelin sheaths in the nerves of pellagrins are evidence that there may be true degeneration of the peripheral nerves in patients suffering from pellagra. The axis-cylinder is affected as well as the myelin sheath, and the involvement of these structures appears to proceed *pari passu*.

Apparently, the larger sheaths are affected more than the smaller in mild neuritis. The presence of large sheaths in neuritis of greater severity might be explained on the basis of swelling in degenerating nerve. Evidence for this is that many of the larger myelin sheaths, instead of appearing as clear-centered rings, were filled with black-stained material (fig. 2 *D* and *E*) and the longitudinal sections of these nerves stained with 1 per cent "protargol" showed a considerable amount of beading and fragmentation and "corkscrew" formation of the axis-cylinders (fig. 3). In some instances of severe neuritis the individual axis-cylinders were separated rather widely.

It is noteworthy that in the few instances in which persons have been imbibing alcoholic liquors heavily and the nerves have been

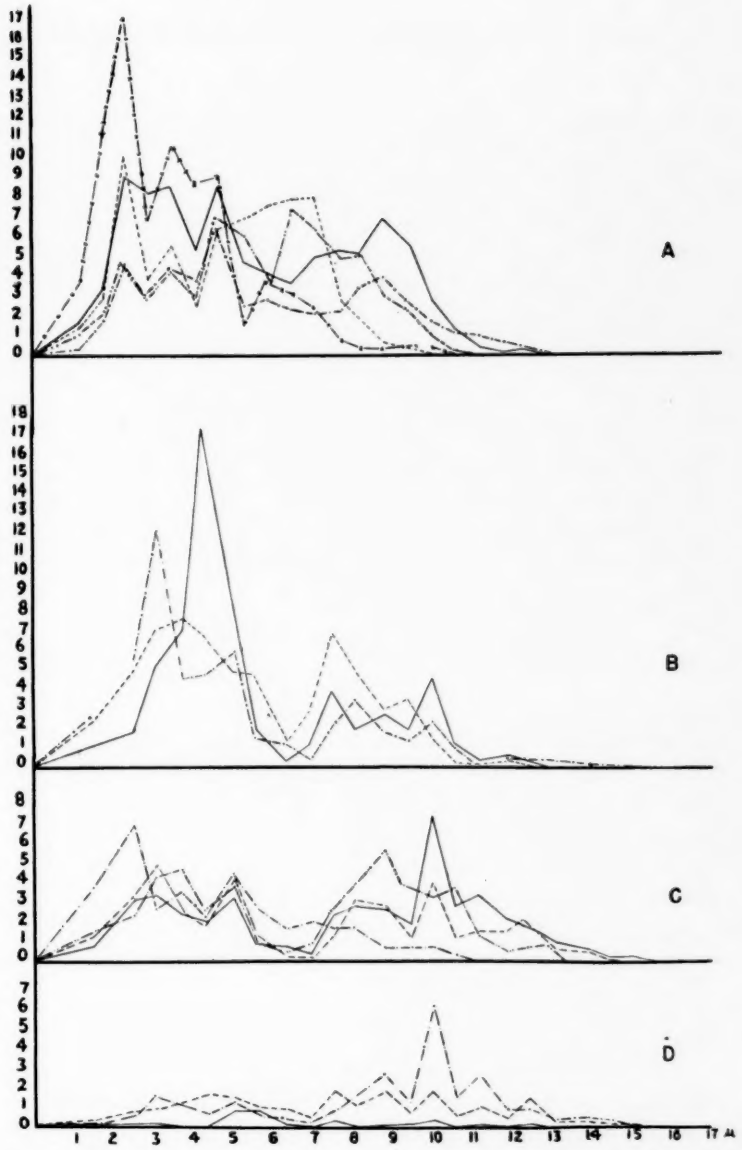

Fig. 1.—Number of myelin sheaths per square millimeter in the peripheral nerves from (*A*) normal persons; (*B*) patients with mild peripheral neuritis; (*C*) patients with moderate peripheral neuritis, and (*D*) patients with severe peripheral neuritis.

In *B*, the solid line represents the curve in case 2; the broken line, the curve in case 3, and the line of dots and dashes, the curve in case 8.

In *C*, the curve in case 5 is represented by a solid line; the curve in case 6, by a broken line; the curve in case 7, by a line of dots and dashes, and the curve in case 9, by a line of dots and two dashes.

In *D*, the curve in case 1 is shown by a solid line; the curve in case 4, by a line of dashes, and the curve in case 10, by a line of dots and dashes.

Ordinates represent the number of myelin sheaths, expressed in hundreds; the abscissas, the size of sheaths in microns.

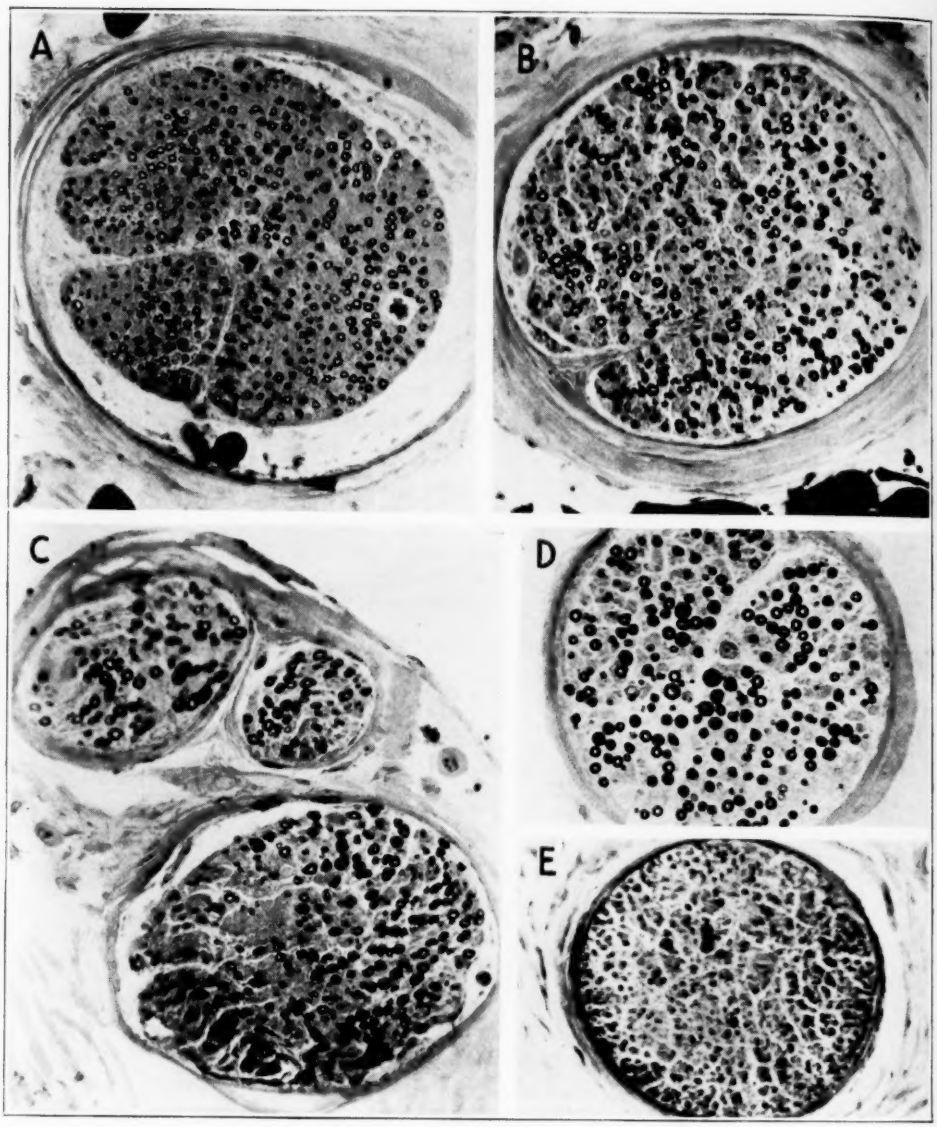

Fig. 2.—Cross sections of the terminal branch of the anterior tibial nerve from 5 patients. Osmic acid stain; × 250.

The number of myelin sheaths per square millimeter of nerve is as follows: *A* (case 13), a control, 6,836; *B* (case 8), a pellagrin, 5,155; *C* (case 11), an alcoholic control, 5,073; *D* (case 10), a pellagrin, 2,674, and *E* (case 1), a pellagrin, 380.

Fig. 3.—Longitudinal section of the terminal branch of the anterior tibial nerve in case 6, stained by the Bodian 1 per cent "protargol" (protein silver) method. Note fragmentation and marked beading of the axis-cylinders. × 275.

examined by the technic used in this study (our cases 1 and 11 and Greenfield and Carmichael's cases 5 and 6[3]) the damage to the nerves has been rather more severe than that in comparable material from persons who do not drink. In case 11, that of a patient with an anxiety state, who consumed liquor to the point that he was considered an alcohol addict, and who had never had symptoms or signs of neuritis, the mean myelin sheath count was considerably lower (25 per cent) than that in any of the other controls in our series and in the group reported by Greenfield and Carmichael.

In 12 patients with nutritional deficiency associated with alcoholism whose cases were previously reported[5] the peripheral nerves studied by the biopsy technic revealed marked loss and degeneration of myelin sheaths. Quantitative counts of myelin sheaths were not made on these nerves. All of these patients had frank signs of neuritis.

This meager evidence would appear to indicate that excess ingestion of alcohol in itself is deleterious to nerves. Nutritional factors surely must be taken into account in an etiologic consideration of alcoholic patients suffering from nutritional deficiency. For 2 of the 4 patients the diet was known to be deficient. The patient in case 11 had an adequate diet. The ingestion of liquor in the latter instance was steady, but rarely enough to cause drunkenness.

There appears to be no exact correlation between clinical findings and morphologic status. In all but 1 of the patients (cases 1, 6, 7 and 10) with myelin sheath counts below 4,000 the tendon reflexes were affected, and in 2 of these (cases 7 and 10) the tendon reflexes were hyperactive. But the presence of normal tendon reflexes may be compatible with a rather low myelin sheath content of the nerve (case 4). However, in this series, the tendon reflexes were never affected when the myelin sheath content of the portion of nerve studied was normal. Spontaneous pain in the legs and tenderness of the muscles of the feet and legs to deep pressure were universal in these cases. Since normal myelin sheath counts were obtained in 2 of them (cases 2 and 3), these factors would not necessarily appear to be signs of neuritis. Although pain and muscle tenderness may not be indubitable indications of neuritis, these symptoms are usually present in cases in which there is a reduced number of myelin sheaths in the nerve. All of the 10 pellagrins showed reduction in sensation of one kind or another, particularly in the feet and legs. Obviously, the so-called stocking type of mild diminution in the appreciation of pain may occur in the presence of a relatively normal myelin sheath content of the nerve.

It becomes clear that no single clinical sign can be correlated with the number of myelin sheaths remaining in the nerve. It must be

5. Aring, C. D.; Evans, J. P., and Spies, T. D.: Some Clinical Neurologic Aspects of Vitamin B Deficiencies, J. A. M. A. **113**:2105-2109 (Dec. 9) 1939.

remembered that only a small bit of peripheral nerve was examined in these patients. It is possible that a representative picture of the whole nerve is not obtained by the biopsy method.

It has been our experience that the neuritis which can be unequivocally associated with uncomplicated nutritional deficiency is rather readily reversible, a feature which does not pertain in the paralytic neuritis associated with ingestion of alcohol. This fact, added to the incidence of few cases of paralytic polyneuritis in the "pellagra belt," at present prevents any convincing generalization on the causation of polyneuritis. There must be some common underlying factor in all neuritis, and it seems reasonable that nutritional deficiency should act as one of the precursors of the basic agent, as does, for example, diphtheria or triorthocresyl phosphate.

SUMMARY

Peripheral nerves from pellagrins and from persons who had no evidence of nutritional deficiency were compared microscopically.

It was found that the myelin sheaths were reduced in number in 8 of 10 persons with pellagra. The axis-cylinders were involved in the process, usually in the same severity as the myelin sheaths. The myelin sheath loss was extreme in the pellagrin who was addicted to alcohol. One person addicted to alcohol and free from signs of neuritis had a comparatively low myelin sheath content of the peripheral nerve.

The study of the morphologic changes in peripheral nerves leaves much to be desired in the analysis of the syndrome of neuritis. Mild clinical signs may occur in the face of an apparently normal myelin sheath content of the nerve. It is conceivable that a small sample of nerve may not indicate the condition of the whole nerve, from its origin in the anterior horn to its termination.

At present, the accurate diagnosis of minimal neuritis is difficult and should be made with care. Deviation of the tendon reflexes from normal is probably the most reliable single sign of peripheral neuritis. Spontaneous pain and muscle tenderness in the limbs may be present when the myelin sheath content of the nerve is normal.

REPORT OF CASES

CASE 1.—A Negress aged 27, weighing 116 pounds (52.6 Kg.), preferred admission to the Hillman Hospital, on June 13, 1940, rather than the alternative of going to jail. She had been drinking large quantities of alcohol since 1930 and had consumed an average of about 1 to 1½ quarts (946 to 1,420 cc.) of corn whisky a day. She stated that her first attack of pellagra occurred in the autumn of 1938. She had had subsequent attacks in the spring of 1939 and 1940. Her recent diet had been grossly deficient in all of its elements. The symptoms of nutritional or neurologic import were pain in the arms, legs and abdomen, nervousness, insomnia, hallucinations, dizziness, tinnitus, soreness of the tongue and lips,

anorexia, vomiting, diarrhea, weakness of the legs and fatigability. She had weighed 140 pounds (63.5 Kg.) in 1936. The significant signs were redness of the tongue and lips, symmetric dermatitis of the hands and feet, moderate tenderness of the soles and marked tenderness of the calves, diminution in appreciation of vibration in the ankles, marked diminution of vibration sense in the knees and some loss of touch and pain perception in the feet and legs. The tendon reflexes were normal with the exception of the ankle jerks, which were not obtained. There was generalized weakness of the lower extremities. She was unable to walk. She was fairly cooperative, but was dull and confused, disoriented as to time and confabulated.

She was given large doses of nicotinic acid, and the signs and symptoms of pellagra improved. The neuritis remained unchanged. A specimen of nerve was taken for biopsy on June 20. Thereafter thiamine hydrochloride was administered intravenously until she was discharged from the hospital, able to walk, on July 30. The spontaneous pain in the legs cleared under this therapy. The tenderness and weakness of the legs gradually improved. The ankle jerks were not obtained during the stay in the hospital.

The patient was placed on a vitamin B–free diet from June 20 through June 28. She excreted 65 micrograms of thiamine in the urine in twenty-four hours on June 20. Fifty milligrams of thiamine hydrochloride was administered intravenously on each of the following days: June 21, 22, 25, 26 and 27. The urinary excretion of thiamine was measured as follows: June 21, 16,400 micrograms; June 22, 17,080 micrograms; June 26, 40,800 micrograms, and June 27, 11,320 micrograms.

The clinical diagnosis was pellagra, polyneuritis, Korsakoff's psychosis and chronic alcoholism. Laboratory and clinical studies indicated that she had a mild deficiency of iron and riboflavin, a moderate nicotinic acid deficiency and a severe deficiency of thiamine. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 380. The axis-cylinders were involved to a moderately severe degree.

Case 2.—A white woman aged 55, weighing 142 pounds (64.4 Kg.), had attended the nutrition clinic of the Hillman Hospital since August 1939. Her first attack of pellagra had occurred nine years previously. Her husband had the same disease. She had had pellagrous dermatitis when first examined at the clinic. Her recent dietary history indicated deficiency of protein, calcium, phosphorus and vitamins (A, B_1, C and riboflavin). She drank no alcohol. Over the past year she had had the following symptoms and signs referable to the nervous system or to the inadequate nutritional state: soreness of the tongue and stomach, dizziness, occasional nausea and diarrhea, nervousness, burning feet and aching legs, particularly at night. The calves were tender, and it was noted on April 17, 1940 that she had a stocking distribution of diminution of the appreciation of touch in the lower extremities. A specimen of nerve was taken for biopsy on June 21, 1940. At this time she complained of pain in the abdomen and legs and numbness of the legs, and there was mild tenderness of the calves. Otherwise the neurologic examination revealed nothing abnormal. After the biopsy 50 mg. of thiamine hydrochloride was administered by vein daily. The symptoms in her legs cleared readily, and in early July she stated that she had never felt better in the past five years.

The patient was placed on a vitamin B–free diet from June 19 through June 25. The urinary thiamine, measured on June 19 and 21, was 79 and 88 micrograms, respectively. Fifty milligrams of thiamine hydrochloride was administered intra-

venously on June 22 and 23. The thiamine excretion thereafter was as follows: June 22, 2,510 micrograms; June 23, 29,800 micrograms, and June 24, 1,400 micrograms.

The clinical impression was that of mild neuritis. Though she was subject to attacks of pellagra, she had no signs of the disease at the time of biopsy, in June 1940. It was judged that she had a mild thiamine deficiency. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 5,930.

CASE 3.—A white woman aged 45, weighing 100 pounds (45.4 Kg.), had suffered her first attack of pellagra in 1925. The recent dietary history indicated that her intake was deficient in protein, calories and vitamin B_1. She drank no alcohol. Symptoms and signs indicative of nutritional deficiency or neuritis were pain in the legs and abdomen, burning of the mouth, loss of weight, nervousness, generalized weakness, atrophied papillae of the tongue, glove and stocking diminution of touch and pain sensation in the extremities, marked diminution in the appreciation of vibration in the lower extremities and some diminution in the hands and forearms, loss of ability to identify passive changes in position of the toes and tenderness of the calf muscles. The tendon reflexes were normal. The patient also had signs of Wernicke's encephalopathy. A specimen of nerve was taken for biopsy on June 21, 1940. Under treatment with thiamine hydrochloride there was remission of the spontaneous pain and tenderness.

The clinical diagnosis was polyneuritis, pellagra and Wernicke's disease. By various methods she was judged to be moderately deficient in thiamine and mildly deficient in nicotinic acid. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 6,210. The axis-cylinders were affected to a moderately severe degree.

CASE 4.—A white man aged 64, weighing 145 pounds (65.8 Kg.), had been studied at the nutrition clinic since 1938. He had first noted the symptoms of pellagra in 1932 and had had an attack every spring since. The recent history indicated that his diet was deficient in protein, calories, calcium, phosphorus, iron and vitamins. He did not use alcoholic liquors. Symptoms and signs which may be related to nutritional deficiency or neuritis were pain in the legs, burning of the feet, dizziness, anorexia, epigastric burning, weakness, nervousness and fatigability. He had lost 15 pounds (6.8 Kg.) in weight recently. The only signs of neuritis or nutritional deficiency were slight tenderness of the calf muscles and slight, but definite, stocking type of diminution in the appreciation of touch, pain and temperature in the lower extremities. A specimen of nerve was taken for biopsy on June 21, 1940, and thiamine hydrochloride was thenceforth administered by vein. Prompt remission of the tenderness and improvement in sensation in the legs were observed.

The patient was kept on a diet free of vitamin B from June 20 through June 25. On June 20 and 21 the thiamine content of twenty-four hour collections of urine was 134 and 74 micrograms, respectively. On June 22, 50 mg. of thiamine hydrochloride was administered intravenously, and on that day there was 11,200 micrograms of thiamine in the urine.

The clinical diagnosis was mild peripheral neuritis. The patient was judged to be mildly deficient in thiamine. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 2,160. The axis-cylinders were affected to a moderately severe degree.

CASE 5.—A white woman aged 46, weighing 142 pounds (64.4 Kg.), had experienced the first attack of pellagra in 1914. Her recent diet was deficient in iron

and vitamins A and B_1. She drank no alcohol. Symptoms possibly related to neuritis or nutritional deficiency were nervousness, constipation, burning and itching of the skin, weakness and fatigability, burning in the epigastrium and pain in the arms, forearms, legs and feet. Significant signs were mild pellagrous dermatitis of the ankles, injected conjunctivas, tenderness of the calf muscles and mild hypalgesia of the glove and stocking variety below the knees and the wrists. The patient could identify touch and distinguish the head and point of a pin everywhere over the skin of the extremities. The tendon reflexes were normal. A specimen of nerve was taken for biopsy on June 21, 1940, and large doses of thiamine hydrochloride were given by vein thereafter. Prompt remission in the weakness and pain in the extremities followed. Tenderness of the calves cleared rapidly and had disappeared by June 23. The appreciation of pinprick gradually improved in the lower extremities. On June 26 the appreciation of pain was normal in the right lower extremity, and the "level" in the left leg had descended to 15 cm. below the lower border of the patella. She was subjectively much improved by June 26, although some nervousness remained.

The patient was given a vitamin B-free diet from June 19 through June 24. The thiamine excretion in the urine on June 19 was 166 micrograms, and that on June 21 was 106 micrograms. On June 22 thiamine hydrochloride was given intravenously in a dose of 50 mg. On that day the patient excreted 92,600 micrograms of thiamine over a period of twenty-four hours. The reason for this enormous excretion of thiamine after a single dose (50 mg.) of thiamine hydrochloride is not obvious.

The clinical diagnosis was mild pellagra and neuritis. The patient was judged to be deficient in nicotinic acid and thiamine. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 4,500.

CASE 6.—A white woman aged 59, weighing 111 pounds (50.3 Kg.), had been followed in the nutrition clinic since 1938. Her first attack of pellagra had occurred in 1936. The recent dietary history indicated that her food intake was deficient in protein, calories, calcium, phosphorus, iron and all of the vitamins. There was no history of ingestion of alcohol. Symptoms which may be related to neuritis or nutritional deficiency were burning sensation in the epigastrium and tongue, nervousness, insomnia, weakness, fatigability, loss of 14 pounds (6.4 Kg.) in one year, aching of the bones in the arms and continuous spontaneous pain in the legs. Significant signs were scaly dermatitis of the elbows, forearms, hands, shins and feet; injection of the conjunctivas; smooth, red tongue; granular lips; nystagmus; hyperactive tendon reflexes except the ankle jerks, which were usually absent but were occasionally obtained with reenforcement; tenderness in the soles and calves, and mild stocking type of hypalgesia and hypesthesia in the lower extremities, up to the knees. A biopsy specimen of nerve was taken on June 21, 1940, and thiamine hydrochloride was administered by vein thereafter. There occurred rapid remission of the pain in the extremities. Remission of the tenderness and subjective weakness was noted on the day after the specimen for biopsy was taken. On this day the ankle jerks could be obtained only in a kneeling position, but on the following day they became very active and thereafter they were obtainable with the patient in a reclining or a sitting position. The sensory loss had been mild, and though it could not be found after the administration of thiamine hydrochloride, this fact was thought not to be significant of improvement.

The patient was placed on a vitamin B-free diet from June 19 through June 25. On June 19 and 20 the thiamine content of twenty-four hour specimens of urine was 204 and 220 micrograms, respectively. On June 22, 50 mg. of thiamine

hydrochloride was administered intravenously. On that day the patient excreted 11,813 micrograms of thiamine in the urine. On June 24 the excretion was 522 micrograms.

The clinical diagnosis was mild multiple deficiency (neuritis, pellagra and ariboflavinosis). Clinical and laboratory methods showed that the patient was mildly deficient in thiamine, riboflavin and nicotinic acid. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 3,900. The axis-cylinders were involved in a moderate degree.

CASE 7.—A white woman aged 27, weighing 120 pounds (54.4 Kg.), had been studied in the nutrition clinic since 1938. Her first attack of pellagra had occurred nine years previously. The recent dietary history indicated that her intake was deficient in protein, calcium, phosphorus, iron, vitamin A, the vitamin B complex and possibly vitamin C. There was no history of ingestion of alcohol. Symptoms that may be associated with nutritional deficiency or neuritis were burning and itching of the skin, soreness of the tongue and lips, burning sensation in the epigastrium, anorexia, constipation, occasional vomiting, scaling of the skin on the arms and legs, burning of the eyes with lacrimation, insomnia, nervousness, apprehension, headaches, dizziness, memory loss, burning sensation of the face, arms and feet, pain in the legs and arms and generalized weakness. Significant findings were conjunctivitis, slight erosion at the angles of the mouth, erythematous dermatitis of the arms and legs, redness of the tongue with atrophic papillae at the tip, tenderness of the calf muscles, hyperactive tendon reflexes and diminution of the appreciation of touch and pain in a stocking distribution up to the midtibial region of both legs. A specimen of nerve for biopsy was taken on June 21, 1940, and thereafter thiamine hydrochloride was administered in large doses by vein. There was rapid remission of spontaneous pain, and the tenderness of the calves, which persisted longer in the right leg than in the left, gradually improved. The stocking type of hypalgesia had cleared by June 26. She regained some composure and felt stronger. In early July administration of thiamine hydrochloride was discontinued, and there was a prompt relapse to the condition in which she was at the time the biopsy specimen was taken. With the use of thiamine hydrochloride the signs usually associated with neuritis (pain in the extremities, tenderness and diminution in sensation) again improved promptly.

The clinical diagnosis was pellagra, mild neuritis and ariboflavinosis. The patient was judged to be deficient in nicotinic acid to a moderate degree and mildly deficient in riboflavin and thiamine. The mean count of the myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 3,491. The axis-cylinders were affected to a moderate degree.

CASE 8.—A white woman, aged 62, weighing 130 pounds (59 Kg.), had been studied in the nutrition clinic since 1938. The first attack of pellagra had occurred twenty-five years ago, and she expressed the belief that she had had an attack yearly since that time. Her recent dietary history indicated deficiency of intake of protein, calories, calcium, phosphorus, iron, the vitamins of the B complex and vitamin C. She drank no alcohol. The recent complaints that might be attributed to deficiency of nutrition or to neuritis were dizziness, insomnia, nervousness, hallucinations, constipation, daily vomiting, some itching of the skin, cramping pain in the epigastrium, weakness and fatigability and marked pain in the legs and feet and some in the arms. Signs indicative of nutritional or nervous disorders were red, smooth tongue, a wide-based gait, a positive Romberg sign, tremulousness of the upper extremities on volitional movements, marked tenderness of the muscles and nerve trunks of the calves and soles, some tenderness in the muscles of the thighs, forearms

and arms. Pinprick and stroke were perceived as "painful electricity" (hyperpathia) in the legs and forearms. She identified touch and pain correctly everywhere in the extremities, and she noted that there was no diminution in these sensations. The appreciation of vibration was markedly diminished in the legs and somewhat diminished in the hands. The tendon reflexes, with the exception of the ankle jerks, had been hyperactive on many occasions since 1938. In April 1940 the ankle jerks were barely obtainable; in May the right ankle jerk was absent and the left reduced in volume. On June 4 and 25 the tendon reflexes were normally active. On June 26 a specimen of nerve was taken for biopsy, and therapy with intravenous injections of thiamine hydrochloride was begun. There was prompt remission in subjective weakness, pain and dizziness. The nerve and muscle tenderness improved gradually, and on July 3 slight muscle tenderness remained. On that day there was slight swaying in the Romberg position with the eyes closed. She noted that she felt better than at any time since she had begun attending the nutrition clinic, in 1938. Thiamine hydrochloride was then withheld, and the entire syndrome was again precipitated.

On June 25 the patient was placed on a vitamin B-free diet. On June 26 the thiamine excretion in the twenty-four hour specimen of urine was 66 micrograms. On June 27, 50 mg. of thiamine hydrochloride was administered intravenously, and a twenty-four hour collection of urine on that day contained 33,900 micrograms. The vitamin B-free diet was continued through June 28.

The clinical diagnosis was neuritis and mild pellagra. She was judged to be moderately deficient in thiamine and mildly deficient in nicotinic acid. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerves was 5,155. There was slight damage of axis-cylinders.

CASE 9.—A white man aged 56, weighing 145 pounds (65.8 Kg.), was admitted to the Hillman Hospital on May 16, 1940. He had lost about 60 pounds (27.2 Kg.) of weight within recent months and was bleeding from the rectum. Adenocarcinoma of the rectum was found, and a perineal resection and colostomy were performed. His first attack of pellagra developed in the spring of 1939. His recent diet had been deficient in protein, calories, calcium, phosphorus and vitamins of the B complex. He drank no alcohol. Among his symptoms and signs, the following might be attributed to nutritional deficiency or neuritis: pain and a feeling of numbness in the legs, redness of the tongue with atrophic papillae, marked diminution of the appreciation of vibration in the legs and marked tenderness of the nerves and muscles of the legs. The tendon reflexes were normal. A specimen of nerve was taken for biopsy on June 21, 1940, and intravenous therapy with thiamine hydrochloride was started. The spontaneous pain in the legs cleared shortly after the first injection. On June 28 there remained slight tenderness of the calf in the right leg and none in the left.

The clinical diagnosis was carcinoma of the rectum, mild neuritis and pellagra. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 4,780. There was slight damage of the axis-cylinders.

CASE 10.—A Negress aged 28, weighing 86 pounds (39 Kg.), had the first attack of pellagra three years previously and had had at least one attack a year since. Her grandmother also had pellagra. The diet had been deficient recently in protein, calories, calcium, phosphorus, iron and vitamins, particularly of the B complex. She drank no alcoholic liquors. Complaints related to the nutritional deficiency or to neuritis were burning and scaling of the skin, hands and feet, dizziness, pain in the legs and arms, weakness, loss in weight, epigastric pain,

anorexia, diarrhea, insomnia, nervousness and hallucinations. Significant signs were pellagrous dermatitis on the knees, shins, feet, elbows, forearms and hands; smooth, fiery red tongue; cheilitis; conjunctivitis; tachycardia; edema of the feet; generalized weakness; hyperactive reflexes and bilateral Hoffmann responses, and tenderness of the calves and of the biceps muscles of the arms. Testing for vibration or pinprick in the legs caused marked pain (hyperpathia). On July 11, 1940 a specimen of the nerve was taken for biopsy, and 50 mg. of thiamine hydrochloride was administered daily for ten days. This caused prompt remission of the spontaneous pain in the legs.

The clinical diagnosis was a severe mixed vitamin deficiency. She was judged to be most deficient in nicotinic acid and riboflavin and slightly deficient in thiamine, vitamin B_6, vitamin A and iron. The mean count of myelin sheaths per square millimeter in the terminal portion of the anterior tibial nerve was 2,674. There was moderately severe damage to the axis-cylinders.

STUDIES ON THE CORPUS CALLOSUM

II. THE HIGHER VISUAL FUNCTIONS IN EACH HOMONYMOUS FIELD FOLLOWING COMPLETE SECTION OF THE CORPUS CALLOSUM

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The importance of unilateral cerebral dominance in the mechanism of speech has become accepted. However, the role of cerebral dominance in the elaboration of visual perceptions remains in dispute.

The present study is an attempt to elucidate this problem. In 6 cases of epilepsy the corpus callosum was completely sectioned by Dr. William P. Van Wagenen (Van Wagenen and Herren[1]). By this surgical procedure the "subordinate" hemisphere (usually the right), subserving the "subordinate" homonymous field (usually the left), is severed of its connections through the splenium with the dominant hemisphere, which subserves the dominant homonymous visual field. If a unilateral cerebral dominance exists for the mechanism of the higher forms of visual perception one would expect a disturbance of this mechanism in the "subordinate" homonymous visual field. On the basis of this assumption the higher visual functions were tested in each homonymous field before and after complete section of the corpus callosum.

METHODS AND PROCEDURE

In each patient laterality of function was studied in detail in collaboration with Dr. K. U. Smith.[2] Eyedness, or ocular dominance, was determined by the methods of Miles,[3] Dolman,[4] Bryngelson (cited by Fink[5]) and Parson[6] and

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1. Van Wagenen, W. P., and Herren, R. Y.: Surgical Division of Commissural Pathways in the Corpus Callosum: Relation to Spread of an Epileptic Attack, Arch. Neurol. & Psychiat. **44**:740 (Oct.) 1940.

2. Smith, K. U., and Akelaitis, A. J.: Studies on the Corpus Callosum: I. Lateral Dominance in Behavior and Bilateral Motor Coordination in Man Before and After Partial and Complete Section of the Corpus Callosum, to be published.

3. Miles, W.: Ocular Dominance Demonstrated by Unconscious Sighting, J. Exper. Psychol. **12**:113, 1929.

4. Dolman, P.: Tests for Determining the Sighting Eye, Am. J. Ophth. **2**: 867, 1919.

5. Fink, W. H.: The Dominant Eye: Its Clinical Significance, Arch. Ophth. **19**:555 (April) 1938.

6. Parson, B. S.: Lefthandedness: A New Interpretation, New York, The Macmillan Company, 1924.

the alinement procedure of della Porta.[7] Footedness and handedness were investigated by studying laterality preferences in performance of unimanual and bimanual tasks.

Perimetric studies of the visual fields were made before and after operation. The subject was studied for absolute and relative orientation, recognition of size, color and objects and lexia in each homonymous field of vision before and after complete section of the corpus callosum.

Perimetric studies were carried out with a Ferree-Rand type of perimeter. In all the cases reported here the visual fields as tested to small white test objects were normal before and after operation.

Absolute orientation was studied in each homonymous field by requesting the patient to touch the tip of a pencil with each hand while he looked directly ahead at the examiner's nose. Relative orientation was studied by having the patient name which of two objects was nearer or farther away.

Size was studied absolutely and relatively in each homonymous field by requesting the patient to give the dimensions of an object and to state which of two objects was larger or smaller.

Color recognition was studied grossly in each homonymous field by the use of colored cards, 10 cm. square. The colors employed were black, white, red, orange, yellow, green, light blue, dark blue and purple. To test for color blindness in direct gaze, Ishihara charts were utilized. No evidence of color blindness was found in this group of patients.

Object recognition (visual gnosia of Lissauer [8]) was tested in each homonymous field by the use of familiar objects, such as a pipe, comb, pencil, scissors, knife, button, match, eraser or key, and of less familiar objects, such as a reflex hammer, ophthalmoscope, vibration fork or eye dropper.

Letter recognition (visual verbal gnosia) was tested in each homonymous field by the use of wooden letters of an ordinary alphabet toy set standing 4.5 cm. in height. Usually the letter could be recognized only when it was close to the midline and yet beyond the limits of the macular zone (2 to 10 degrees around the point of fixation).

Stereoscopic vision was studied by means of Hecht's [9] box, using red (29) and green (58) filters, and an ordinary stereoscope, using red and green filters for fusion of colors and stereoscopic cards for the fusion of images.

REPORT OF CASES

CASE 1 (hospital unit no. 133774).—F. R., a single white woman aged 26, was admitted to the Strong Memorial Hospital on Feb. 19 and May 23, 1939, with a history of grand mal seizures since the age of 2 years. She had been successfully treated for congenital syphilis. Her intelligence was normal. Physical examination revealed widely separated, peglike teeth and a small uterus. Neurologic examination disclosed Erb's palsy of the left side with atrophy of the left side and absence of the biceps reflex on the same side.

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7. della Porta, G. B.: De refractione, 1593; cited by Scheidemann, N. V.: Psychology of Exceptional Children, New York, Houghton Mifflin Company, 1931, p. 130.

8. Lissauer, H.: Ein Fall von Seelenblindheit nebst einem Beitrag zur Theorie derselben, Arch. f. Psychiat. **21**:222, 1889.

9. Hecht, S.: The Binocular Fusion of Colors and Its Relation to Theories of Color Vision, Proc. Nat. Acad. Sc. **14**:237, 1928.

Visual functions in each field were normal. With glasses visual acuity was 6/15 in the right eye and 6/7.5 in the left eye.

Laterality studies showed she was left eyed but predominantly right handed and right footed.

Operations.—On Feb. 23, 1939 the body and posterior half of the genu were sectioned by Dr. W. P. Van Wagenen. On May 25, 1939 the remainder of the corpus callosum was cut.

Course.—After the first operation left hemiparesis with paresthesias developed. The patient became depressed, and this condition persisted for about six months. No disturbance of visual functions was observed in either visual field after the first operation.

Postoperative Examination.—In September 1939 she was carefully studied. The depression with psychomotor retardation persisted. Laterality studies gave essentially the same results as before operation. The patellar and ankle jerks on the left side were slightly increased. Examination of the visual function revealed no disturbance in either visual field except a little more difficulty in recognizing objects and letters in the left homonymous field.

On subsequent examinations, on Nov. 6, 1939 and Aug. 22, 1940, objects and letters were recognized with equal facility in either homonymous field.

CASE 2 (hospital unit no. 33354).—E. J. B., a deteriorated single white woman aged 24, was admitted to the Rochester Municipal Hospital on March 11, 1939. She had been subject to grand mal seizures since the age of 10 years and for the past six years had been institutionalized on several occasions because of psychomotor attacks. Physical examination revealed facial acne and perforation of the left ear drum. The neurologic findings were normal.

Examination of visual functions disclosed no abnormalities.

Laterality studies revealed right ocular dominance and predominant right handedness and right footedness. As a child she preferred her left hand in eating and writing. Early in school she was forced to write with her right hand and at present is right handed in most tasks.

Operations.—On March 18, 1939 the body and posterior half of the genu were sectioned by Dr. W. P. Van Wagenen. On April 24, 1939 the remainder of the corpus callosum was cut.

Postoperative Examination.—No change in her neurologic status followed either operation. On May 16, 1939 no evidence of disturbance in visual perception could be found in either homonymous field. On subsequent examinations the visual functions remained normal in each homonymous field. Laterality tendencies remained the same as before operation.

CASE 3 (hospital unit no. 85145).—G. B., a mentally retarded white boy aged 14, was admitted to the Rochester Municipal Hospital on May 8, 1939. At the age of 2 years left hemiplegia developed after diphtheria. Shortly after a severe attack of pertussis six years before admission to the hospital, he began having attacks of grand mal and "dizziness," which have become increasingly more severe and more frequent. Physical examination revealed an unusually well developed boy appearing older than his chronologic age. The Stanford-Binet test gave a mental age of 9 years 3 months. Neurologic examination disclosed typical left hemiplegia.

The visual functions were not disturbed in either homonymous field.

Laterality studies showed right ocular dominance, right handedness and right footedness.

Operation.—On May 19, 1939 Dr. W. P. Van Wagenen sectioned the corpus callosum completely. The left limb of the fornix was divided just above the foramen of Monro.

Course.—The neurologic picture remained the same as before operation. The patient continued to have grand mal seizures. On Sept. 26, 1939 examination of the visual functions in each homonymous field revealed no abnormality.

CASE 4 (hospital unit no. 160979).—C. S., a white girl aged 15, was admitted to the Strong Memorial Hospital on Jan. 4, 1940. At the age of 15 months she had encephalitis, after which left hemiplegia occurred. The neurologic status has improved with training, so that she is now able to weave and sew, but has never been able to type or play the piano because the left hand is awkward. At the age of 5 years she became subject to petit mal attacks, and at 10 years grand mal seizures developed, which have increased in frequency. Physically, she was well developed and well nourished. Neurologic examination disclosed residual left hemiplegia, with palsy of the lower part of the face, exaggerated deep tendon reflexes, slight increase in muscle tone and an equivocal extensor response on plantar stimulation. The left arm exhibited occasional athetoid movements, and in walking associated movements in this extremity were absent. Her gait was unsteady, with a tendency to walk to the left.

Visual functions were not disturbed in either homonymous field.

Laterality studies showed left ocular dominance, right handedness and right footedness.

Operation.—A right frontoparietal craniotomy was performed by Dr. W. P. Van Wagenen on Jan. 22, 1940, and the corpus callosum was completely sectioned. The cortex showed a moderate amount of atrophy, but no scar tissue was noted.

Course.—There developed left-sided dyspraxia with forced motor innervation in the left hand, left-sided astereognosis and left tactile alexia, which subsequently cleared.

Postoperative Examination of Visual Functions.—On Jan. 29, 1940 she was able to point correctly with her right hand to objects in either homonymous field. Relative orientation and appreciation of size, color, objects and letters were intact in each homonymous field. Stereoscopic fusion of colors and images was intact. She was able to fuse colors with the Hecht apparatus satisfactorily. On subsequent tests, one month and six months later, these visual functions remained intact.

CASE 5 (hospital unit no. 93283).—E. C., a white boy aged 13, was admitted to the Strong Memorial Hospital on Jan. 1, 1940. At the age of 6 years, after scarlet fever, he began to have petit mal attacks. Two years before admission grand mal attacks developed, and recently he had become a behavior problem. Physical examination revealed enlarged tonsils and carious teeth. There were slight weakness of the lower right side of the face, pseudoathetoid movements of both hands, a tendency to assume a preoccupied, mildly cataleptic attitude and a questionable extensor response of the large toe bilaterally on plantar stimulation.

Visual acuity was 6/30 in the right eye and 6/7.5 in the left eye. With glasses this was corrected to 6/6 in each eye. Visual fields were full. The visual functions were not disturbed in either homonymous field.

Laterality studies showed right ocular dominance, right footedness and predominant right handedness in unimanual and bimanual tasks. The father was predominantly left handed and left footed. In tests for ocular dominance, the father was right eyed in the Bryngelson, Parson and Miles tests and left eyed in the Dolman test and was unable to aline consistently in the Porta test.

Operation.—On Feb. 19, 1940, Dr. W. P. Van Wagenen sectioned the corpus callosum completely.

Postoperative Course.—The patient had numerous jacksonian and "terror-like" seizures for one month after operation. He displayed a variable neurologic picture from day to day, but right-sided paresis was consistently present.

Postoperative Examination of Visual Functions.—On March 19, 1940 the visual fields were full at all angles to small test objects and recognition of size, color, objects and letters was intact in each homonymous field. Relative orientation was similarly intact. Owing to the paresis of the right arm, one could only test absolute orientation in each field by having the patient touch the object with his left hand, and this he did correctly.

CASE 6 (hospital unit no. 131559).—G. E., a married white man aged 35, was admitted to the Strong Memorial Hospital May 2, 1940 and was discharged June 23. At the age of 14 years he had poliomyelitis, which left him with weakness of the right leg. At the age of 28 osteomyelitis of the right tibia developed, and at the age of 32 he became aphasic and paralyzed on the right side as a result of a left frontoparietal abscess. This was successfully drained by Dr. Van Wagenen on Sept. 3, 1937, and the paralysis and aphasia cleared up. However, since then he had been subject to grand mal convulsions, which were manifested by unconsciousness and generalized seizures, more marked on the right side. After a seizure he was aphasic and the right arm was lifeless for several hours. In 1939 a mid thigh amputation of the right leg was performed, from which he convalesced satisfactorily.

Neurologic examination revealed hesitating speech suggestive of stutter and mild emissive aphasic disorder, absence of the right corneal reflex and reduction of hearing in the left ear, with bone conduction better than air conduction. The deep reflexes in the right upper extremity were slightly exaggerated.

Examination of visual functions revealed no abnormalities.

The right eye was dominant. He was predominantly right handed in unimanual and bimanual tasks. Before the amputation he preferred his right foot in kicking. Left cerebral dominance was well illustrated in this case, in which aphasia developed with right hemiplegia in 1937.

Operation.—A right frontoparietal craniotomy was performed by Dr. Van Wagenen on May 17, 1940. The corpus callosum was completely sectioned.

Postoperative Course.—The patient convalesced rapidly and without complications. Neurologic examination on June 5, 1940 revealed the same status as before operation.

Postoperative Visual Functions.—The visual fields were normal in size. Absolute and relative orientation in the right and left homonymous fields was intact. Size and color appreciation was intact in each homonymous field. Similarly, he had no difficulty in recognizing objects and wooden letters in either field. Stereoscopic vision was not impaired.

COMMENT

The question naturally arises as to how complete is the isolation of each occipital and parietal lobe from the other when the corpus callosum is completely sectioned. The possible role of other interhemispheral commissures must be considered.

The anterior commissure consists of an olfactory and a neopallial portion. The olfactory portion can be ignored in the present discussion.

The termination of the fibers forming the neopallial portion has not been definitely determined. Popoff [10] observed complete degeneration in the neopallial portion of the anterior commissure in a case in which bilateral lesions of the lingual lobe and the adjacent cuneus, the fusiform lobe and the posterior part of the hippocampus were present. Flechsig [11] found less complete degeneration of the anterior commissure in a case in which a unilateral lesion involved the same areas as those Popoff described. Dejerine,[12] studying 5 cases of his own and the 2 cases of Henschen, concluded that lesions in this area do not produce degenerations in the anterior commissure. He expressed the belief that the anterior commissure contains fibers from the olfactory cortex and the anterior portion of the temporal lobe. He described the variable results of different investigators obtained by methods of dissection. Sunderland [13] found degenerations in the anterior commissure only after extirpation of the temporal lobes in monkeys. The evidence, although meager, suggests that the anterior commissure does not carry interhemispheral fibers from the parietal and occipital lobes.

The hippocampal commissure deals entirely with interhemispheral fibers connecting the hippocampi. According to Collier,[14] the posterior commissure probably contains fibers concerned in associated movements of the eyes. Sunderland [13] found degeneration in the septum pellucidum following occipital lesions in monkeys; the possibility of such interhemispheral connections in man should be considered, but it would seem reasonably certain that they are few and of relatively little importance. Thus one is led to conclude that a complete section of the corpus callosum severs fairly completely the interhemispheral connections between the occipital and parietal lobes of one side and those of the other.

In this series of patients left cerebral dominance appeared to predominate as far as studies of handedness and footedness could be utilized. In only 2 patients (cases 1 and 4) was left ocular dominance present. After complete section of the corpus callosum ocular dominance remained unchanged in each patient. In this small group the incidence of right handedness and left eyedness was 33.3 per cent, which was higher than the 13 per cent reported by Mills [15] for the population at

10. Popoff, cited by Dejerine.[12]

11. Flechsig, cited by Dejerine.[12]

12. Dejerine, J.: Anatomie des centres nerveux, Paris, Rueff & Cie, 1895, vol. 1, p. 805.

13. Sunderland, S.: The Distribution of Commissural Fibers in the Corpus Callosum in the Macaque Monkey, J. Neurol. & Psychiat. **3**:9, 1940.

14. Collier, J.: Nuclear Ophthalmoplegia, with Special Reference to Retraction of the Lids and Ptosis and to Lesions of the Posterior Commissure, Brain **50**: 488, 1927.

15. Mills, L.: Unilateral Sighting, California & West. Med. **28**:189, 1928.

large. Parson [6] claimed that left eyedness exists in about 30 per cent of the population and suggested that left handedness or right cerebral dominance is inherited as a mendelian recessive factor. Since each retina is represented in both hemispheres, it is difficult to assume that ocular dominance has an anatomic basis on which cerebral dominance may be studied. This question has never been adequately answered by students of laterality and I believe does not warrant further consideration here. That handedness is usually accompanied by a corresponding keenness of optic, acoustic and tactile impressions on the same side is accepted by most investigators. Nielsen [16] concluded that for the visual recognition of objects one occipital lobe is dominant over the other. Although the left hemisphere is usually the dominant one, the right may be dominant, even in right handed people. However, in this series it is possible to study the potentialities of each hemisphere when isolated from the other irrespective of which hemisphere may be dominant.

Absolute and Relative Orientation of Objects (geometric optic absolute gnosia).—In his studies of 8 soldiers with gunshot wounds of the head involving the posterior and upper parts of both parietal lobes, Holmes [17] found that these patients were unable to recognize the position of objects seen in central or peripheral vision and that their estimation of distance was most severely involved. Generally this difficulty was more evident in the peripheral fields. Similarly, their ability to localize the relative position of two or more objects which were in vision at the same time was disturbed. Riddoch [18] reported 2 cases of visual disorientation in the right homonymous half-fields with no difficulty in central vision or in the left homonymous fields. In both cases a tumor was found in the left parietal lobe involving the angular and supramarginal gyri. From the study of this series of 6 patients the conclusion is justified, I believe, that absolute and relative orientation of objects is a function represented in each cerebral hemisphere. Similarly, no evidence of visual inattention was observed in either homonymous field after section of the corpus callosum.

Recognition of Size.—Holmes's patients showed a disturbance for the absolute and relative lengths and sizes of objects. The results of study of this series would indicate that the ability to recognize size visually is represented in each hemisphere.

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16. Nielsen, J. M.: Unilateral Cerebral Dominance as Related to Mind Blindness: Minimal Lesion Capable of Causing Visual Agnosia for Objects, Arch. Neurol. & Psychiat. **38**:108 (July) 1937.

17. Holmes, G.: Disturbances of Visual Space Perception, Brit. M. J. **2**:230, 1919.

18. Riddoch, G.: Visual Disorientation in Homonymous Half-Fields, Brain **58**:376, 1935.

Recognition of Color.—In spite of numerous observations, no definite evidence as to the cortical representation of the color sense has been obtained. Holmes [19] asserted that an isolated loss or dissociation of color vision was not produced by cerebral lesions. Wechsler,[20] reviewing the literature, was led to conclude that color perception occurred in the third and fourth lamina of the calcarine region. Best [21] assumed the existence of a *Farbfeld* in the left hemisphere. The conclusion to be drawn from observations in this series of cases is that the ability to recognize colors is equally well represented in each hemisphere. The colors appeared of the same intensity in each visual field after complete section of the corpus callosum.

Recognition of Objects (visual gnosia of Lissauer [8]).—Nielsen [16] reviewed the work of previous investigators and, in collaboration with Von Hagen,[22] reported cases of his own. The role of cortical dominance in this function has never been adequately answered. The results obtained from this study suggest that the ability to recognize concrete objects is represented in each hemisphere.

Recognition of Letters (visual lexia or verbal gnosia).—Henschen [23] concluded from his careful clinicopathologic studies that destruction of the left angular gyrus always produced word blindness. It is of course impossible for the subject to read printed words in the periphery of the visual field, but it is possible to recognize individual letters of the alphabet in that portion of the field reasonably outside the area of macular vision which varies from 2 to 10 degrees around the fixation point. This macular zone is preserved in the hemianopic field after section of the splenium of the corpus callosum (Hyndman [24]). If the subject is given the individual letters of a word in succession he is able to recognize the word. The fact that these patients are able to perform this function in either homonymous visual field as easily after complete section of the corpus callosum as before suggests that each hemisphere possesses the mechanism for visual lexia.

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19. Holmes, G.: Disturbances of Vision by Cerebral Lesions, Brit. J. Ophth. **2**:353, 1918.

20. Wechsler, I. S.: Partial Cortical Blindness with Preservation of Color Vision, Arch. Ophth. **9**:957 (June) 1933.

21. Best, F.: Ergebnisse der Kriegsjahre für die Kenntnis der Sehbahnen und Sehzentren, Zentralbl. f. d. ges. Ophth. **3**:193 and 241, 1920.

22. Nielsen, J. M., and Von Hagen, K. O.: Three Cases of Mind Blindness (Visual Agnosia), J. Nerv. & Ment. Dis. **84**:386, 1936. Nielsen, J. M.: Dominance of the Right Occipital Lobe, Bull. Los Angeles Neurol. Soc. **5**:135, 1940.

23. Henschen, S. E.: On the Function of the Right Hemisphere of the Brain in Relation to the Left in Speech, Music and Calculation, Brain **49**:110, 1926.

24. Hyndman, O. R.: The Central Visual System: Evidence Against Bilateral Representation Through the Splenium of the Corpus Callosum, Arch. Neurol. & Psychiat. **42**:735 (Oct.) 1939.

Stereoscopic Vision.—In view of the fact that stereoscopic vision is not disturbed in patients with complete homonymous hemianopia, it is not surprising that these patients were capable of fusing colors and images stereoscopically after operation.

As far as I can find in the literature, only the case reported by Trescher and Ford [25] deals with a study similar to that reported here. In this case, after section of the posterior half of the corpus callosum, visual agnosia and alexia were found in the left homonymous field. It must be emphasized that the patient had internal hydrocephalus, a Korsakoff-like syndrome for several weeks after operation and disorientation for space. Just how much injury to the nervous system besides the section of the corpus callosum was produced in the removal of the tumor is difficult to determine. In the series reported here symptoms of a Korsakoff syndrome were absent.[26]

SUMMARY AND CONCLUSIONS

In 6 epileptic patients in whom the corpus callosum was completely sectioned the higher visual functions in each homonymous field were studied. No disturbance of absolute or relative orientation, absolute or relative discrimination of size or recognition of color, objects or letters was found in either homonymous field of vision.

These findings suggest (1) that the mechanisms for these visual functions reside within each hemisphere or (2) that subcortical commissural systems provide a sufficient interplay between the two hemispheres to allow control of the "subordinate" hemisphere by the dominant hemisphere. In view of present knowledge this explanation is improbable.

Consequently, this investigation furnishes no support for the theory that a unilateral cerebral dominance exists in the elaboration of visual perceptions.

25. Trescher, J. H., and Ford, F. R.: Colloid Cyst of the Third Ventricle: Report of a Case; Operative Removal with Section of Posterior Half of Corpus Callosum, Arch. Neurol. & Psychiat. **37**:959 (April) 1937.

26. Akelaitis, A.: Psychobiological Studies Following Section of the Corpus Callosum: Preliminary Report, Am. J. Psychiat., to be published.

DULNESS AS AN EPILEPTIC EQUIVALENT

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THE VARIETIES OF "EPILEPTIC DETERIORATION"

The idea that mental deterioration is a regular accompaniment of convulsions is all too firmly rooted in the minds of the public and of many physicians. Recent studies show, on the one hand, that mental deterioration occurs in only a minority of patients suffering from convulsions [1] and that, on the other hand, when it does occur, it is often associated with evidences of widespread progressive cerebral atrophy.[2]

So-called epileptic deterioration is sometimes ascribed to the use of anticonvulsant drugs. Careful observations show that in at least the great majority of cases the long-continued use of phenobarbital and bromides does not affect the mind, even after years of continuous treatment.[1] Either of these standard drugs will, of course, produce somnolence and apathy if given in large doses, and often if given in therapeutic doses, but this is obviously a temporary matter.

The fact of living under the constant threat of convulsions is manifestly a heavy psychologic burden. It is apt to result in emotional tensions and to lead to a feeling of hopelessness, which tinges intellectual processes and renders concentration difficult. A specific "epileptic

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1. Lennox, W. G.: The Non-Institutional Epileptic, A. Research Nerv. & Ment. Dis., Proc. (1929) **7** (pt. 2):358-372, 1931. Paskind, H.: Absence of Deteriorating Effects of Bromides in Epilepsy, J. A. M. A. **103**:100-103 (July 14) 1934.

2. Hodskins, M. B., and Yakovlev, P. I.: Pathologic Contribution to Concept of Neurosomatic Deterioration in Epilepsy, with Record of Two Cases, Am. J. Psychiat. **10**:663-666, 1931.

personality" has been described,[3] and it has been suggested that psychologic conflicts may form a part of the chain of events leading to an attack.[4]

Some seizures may take the form of abnormal conduct, the so-called psychic equivalents, or psychomotor attacks. During them, the patient may suddenly stop what he is doing and launch into an irrational, occasionally destructive activity, for which he has often no memory, or only a hazy one, afterward. Unexplained bursts of temper, tantrums and occasionally long periods of amnesia may be thus produced. Certain psychoses [5] and behavior disorders [6] in children seem to consist of a series of such seizures, sometimes with no other manifestations of "epilepsy."

These four varieties of interference with normal emotional and intellectual functions are well recognized by all who come into contact with many patients suffering from convulsions. The purpose of this communication is to point out that there may be a distinct fifth type, possibly more prevalent than any of the others, which appears not to have been clearly described.

This fifth type of disturbance of intellectual function is one in which the entire attack remains subliminal, unnoticed by either the patient or those about him, and of course unaccompanied by unconsciousness or motor or sensory disturbance. It is well recognized that brief "absences" may occur as often as several times a day in some cases, without seriously interrupting the patient's occupation or ability to concentrate. If, however, literally myriads of even milder attacks of the same type occur almost continuously over substantial periods, their effect may be crippling to any complicated form of mental activity.

How can such disturbances of the intellect be clearly distinguished from "epileptic deterioration," depression by drugs or the results of anxiety?

The most objective method of differentiation is by means of electroencephalographic records. Schwab [7] has produced graphic evidence that bursts of subliminal dysrhythmias, usually of the petit mal or psycho-

3. Clark, L. P.: Clinical Studies in Epilepsy, Utica, N. Y., State Hospital Press, 1917.

4. Fremont-Smith, F.: Influence of Emotion in Precipitating Convulsions, Am. J. Psychiat. **13**:717-723, 1934.

5. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Likeness of the Cortical Dysrhythmias of Schizophrenia and Psychomotor Epilepsy, Am. J. Psychiat. **95**: 256-269, 1938.

6. Jasper, H. H.: Solomon, P., and Bradley, C.: Electroencephalographic Analyses of Behavior Problem Children, Am. J. Psychiat. **95**:641-658, 1938.

7. Schwab, R. S.: Method of Measuring Consciousness in Attacks of Petit Mal in Epilepsy, Arch. Neurol. & Psychiat. **41**:215-217 (Jan.) 1939.

motor type, are regularly accompanied by a prolongation of the patient's reaction time in voluntary response to a signal. Electroencephalographic records were taken in all of the cases to be described, and there was a high degree of correlation between the periods of dulness and the periods of abnormal electrical activity. Occasionally, the intellectual handicap is so brief and vivid to the patient that he is aware he has experienced it (for example, after overventilation) and it can be correlated with the electroencephalographic findings.

Another, in some ways more crucial, criterion is the effect of treatment with an anticonvulsant (dilantin sodium) which is not soporific. Patients who are transferred from phenobarbital to dilantin sodium often remark on their increased alertness and the improvement in their ability to work (Merritt and Putnam,[8] Kimball and Horan [9] and others). An astonishing example is the case reported by Fabing and Twitchell-Alen.[10] But so also, on the other hand, do some patients with relatively infrequent attacks who have not previously received any medication, after they become adjusted to phenobarbital (Robinson and Osgood [11] and others).

Finally, a detailed history will often reveal characteristics of the intellectual handicap which create at least a presumption as to the nature of the disturbance.

The existence of periods of dulness of this general type has doubtless been noticed by many epileptologists and the disturbance classified as a variety of psychic equivalent, but it has apparently not received intensive study. Schroeder van der Kolk [12] gave an undoubted example and remarked: "From this case it is particularly clear, that idiocy, or apparent dementia after epilepsy, is quite a different disease from dementia after idiopathic mania . . . which is incapable of cure." It has not been mentioned at all by such authorities as Esquirol, Foville

8. Merritt, H. H., and Putnam, T. J.: Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, J. A. M. A. **111**:1068-1073 (Sept. 17) 1938.

9. Kimball, O. P., and Horan, T. N.: The Use of Dilantin in the Treatment of Epilepsy, Ann. Int. Med. **13**:787-793, 1939.

10. Fabing, H. D., and Twitchell-Alen, D.: The Case of Eugene Z.: A Preliminary Report, read before the Section on Convulsive Disorders of the American Psychiatric Association, Cincinnati, May 20, 1940.

11. Robinson, L. S., and Osgood, R.: Comparative Effects of Phenobarbital and Dilantin Sodium in the Treatment of Epilepsy, J. A. M. A. **114**:1334-1335 (April 6) 1940.

12. Schroeder van der Kolk, J. L. C.: On the Minute Structure and Functions of the Spinal Cord and Medulla Oblongata, and on the Proximate Cause and Rational Treatment of Epilepsy, translated by W. D. Moore, London, New Sydenham Society, 1859, p. 272.

and Sieveking. The following description of the "interparoxysmal mental state" by Gowers [13] evidently refers to the phenomenon in question:

> The mental state of epileptics, as is well known, frequently presents deterioration, and this constitutes one of the consequences of the disease which is most dreaded . . . In its slighter form there is merely defective memory, especially for recent acquisitions . . . In . . . cases . . . which constitute a majority of the whole, the [mental] failure must be regarded as a consequence of the disease. It distinctly succeeds the fits in points of time, and may lessen very much when the fits are arrested by treatment.

Spratling [14] slightly extended Gowers' description as follows:

> We class the effects of epilepsy on the mind . . . in point of time as temporary, prolonged, or permanent. The temporary effects include transitory states of disturbance that appear with he convulsion, are inseparable from it, because they are essentially a part, and disappear with it. Inter-paroxysmal mental states due to epilepsy: 1. Transitory ill-humor and simple loss of memory for recent events; in other cases, for events regardless of the time of their occurrence. To these we must add as pronounced adjuncts of the epileptic's mental peculiarities: emotional irritability, impulsiveness, moral anergia, and incapacity for any form of valuable productive occupation dependent on initiative in conception and consecutive activity. 2. Slight clouding or dulling of the intellect, as a whole, which often becomes more pronounced just before the fit. 3. Feeble-mindedness.

It will be seen that Spratling had difficulty in distinguishing the temporary mental incapacity from an aura or affective psychic disorders, on the one hand, and permanent deterioration, on the other.

No actual case reports were given by Schroeder van der Kolk, Gowers or Spratling.

REPORT OF CASES

The first case in which the existence of temporary mental dulness was suspected on the basis of cerebral dysrhythmia was the following:

> CASE 1.—P. J., an intelligent and well educated man of 32, began having convulsions of the grand mal type six years ago. His attacks have always followed a surprisingly exact schedule, occurring every two months with great regularity. At the corresponding time in the intervening month, and for two to three days before one of his grand mal attacks, the patient finds himself distinctly slow and dull. He lacks initiative, in contrast to his normal alert and active attitude. He is unable to read a long and complicated story with understanding or to undertake a moderately complicated problem of any kind. While he can do simple arithmetic during these dull periods, such a problem as multiplying a four digit number by a one digit number is a formidable task for him. He has noticed a

13. Gowers, W. R.: Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms and Treatment, New York, William Wood & Company, 1885, p. 101.

14. Spratling, W.: Epilepsy and Its Treatment, Philadelphia, W. B. Saunders Company, 1904.

tendency to transpose digits in reading numbers. At such times he is entirely conscious and oriented and emotionally stable. Neither then nor at other times does he have petit mal attacks or emotional outbursts.

Repeated physical and neurologic examinations have revealed no abnormalities. The results of elaborate laboratory studies were normal, except for the electroencephalographic findings.

This patient has been subjected to an extensive electroencephalographic study during the past three years. Records taken daily by Dr. F. A. Gibbs when the patient was receiving no treatment showed a gradually increasing abnormality as the time of month for the convulsion approached (fig. 1). The abnormality would last for about five days, whether a convulsion occurred or not.

The patient has undergone various forms of treatment, including a drastic regimen of dehydration, with little relief. For the past two years he has been taking dilantin sodium, 0.4 Gm. daily, and has had only one convulsion. The periods of dulness still occur, usually accompanied by a migrainous headache, and are accompanied by dysrhythmia, but are far shorter and milder than formerly.

In this case the various distinguishing features of periodic dulness are well illustrated. First, more complete electroencephalographic

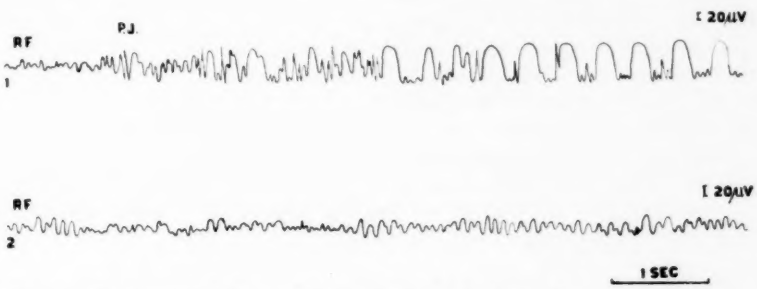

Fig. 1.—Electroencephalographic record of P. J. (case 1).

1, record taken from the right motor region during a period of intellectual dulling without overt manifestations, the day before a seizure. Note the wave and spike pattern.

2, record taken during a period of mental normality between seizures. (Permission of Dr. F. A. Gibbs.)

evidence was obtained than would ordinarily be possible. Second, the variation of the symptom with proper medication was unmistakable. Third, the patient was an excellent observer and could give a first rate account of the characteristics and intermittency of the symptoms.

CASE 2.—D. W., aged 30, formerly a lineman, was seen in consultation with Dr. Kate Constable and is reported by her permission. On June 21, 1929 the patient sustained a fracture of the right parietal bone. He returned to work after two months, but complained of dizziness. A year later a personality change was noticed, with depression.

In July 1932 he began having generalized convulsions. Their frequency varied, increasing on the whole but averaging two to three a month. Neurologic examination showed slight unsteadiness in standing, a little drooping of the right side of

the mouth and slight weakness of the right external rectus muscle. Encephalograms (August 1932) showed symmetric dilatation of both ventricles, without evidence of cortical atrophy. Lumbar puncture (May 1933) showed an initial pressure of 150 mm. Examination of the fluid showed nothing abnormal. The results of a dextrose tolerance test (March 1934) were well within normal limits. These examinations and laboratory tests were repeated at intervals, without yielding additional evidence.

Of particular interest are the psychometric tests (all performed by Miss Gladys Tallman). The first, made on Aug. 5, 1932, showed an intelligence quotient of 0.91, which placed him in the average intelligence group. The test was repeated on Aug. 11, 1932, Dec. 11, 1933, March 8, 1935 and March 9, 1938, with practically identical results.

The patient had three severe falls during attacks in 1935 and may have sustained a further injury to the head.

An electroencephalographic study was performed on Oct. 14, 1938 by Dr. Hans Strauss. Many 3 per second waves, increased by hyperventilation, were demonstrated. This record, unfortunately, is not available.

The patient was given a number of different types of treatment. The first was administration of phenobarbital in amounts up to 1½ grains (0.097 Gm.) daily, with intermissions throughout the course of the disease. He was also given other barbiturates irregularly. He was vigorously dehydrated by limitation of fluids, administration of magnesium sulfate by mouth, theobromine with sodium salicylate and a ketogenic diet, which produced acidosis and brought the specific gravity of the urine to 1.027. This produced slight improvement, but only over a few months. In 1933 treatment by repeated lumbar punctures and air insufflations was begun.

In October 1938 the patient was given dilantin sodium, 0.3 Gm. daily, but gastroenteritis (possibly due to food poisoning) developed, so that the medication had to be interrupted. Dilantin sodium was administered again, beginning in March 1939, and the amount was gradually increased to 0.3 Gm. daily, without particular improvement.

The patient was seen by one of us on Oct. 27, 1939, and the following note was made:

"The patient informs me that he has been subject to petit mal attacks at frequent intervals ever since the onset of the disease. During these, he loses consciousness for a moment but then is able to go on with the conversation or whatever he has been doing.

"In addition to these attacks, he has for the last six months been aware of a milder, but almost continuous, disturbance of his mental faculties. He is aware of what is going on around him, but is frequently slightly disoriented or forgetful. Thus, while at another hospital, he saw a doctor whom he knew well but could not remember who he was. He often confused two of the nurses who were in constant attendance on him. He would start out to do a thing e. g., to carry a note to some one, and on the way would forget what he had started out to do. These symptoms seem to exist irrespective of medication, though it is possible he does not remember accurately what medication he has had.

"He states that he has felt continuously groggy and dull for the same period; his head swims and aches, and he walks like a drunken man. I could make out no particular ataxia or tremor on brief examination.

"His wife states that he has undergone a definite character change, chiefly an intellectual deterioration. He never was much of a reader. She describes his mental disability as consisting mainly of loss of memory.

"The impression is that the patient's mental disturbance may be a true "organic" deterioration. It may, however, represent frequent mild interruptions of consciousness by dysrhythmia."

The dose of dilantin sodium was increased to 0.4 Gm. a day, and phenobarbital was then omitted. With the dosage at this level, he had only two attacks in the following three months. A note dated Feb. 19, 1940 states:

"He felt so much better that he was able to go outdoors and work around the place. He spontaneously volunteered the information: 'Since taking more of the capsules I have felt better able to concentrate and more ambitious to do things.'"

It was also felt there was a decided change in the patient's bearing and manner. Instead of being apathetic and shy, as at a previous interview, he seemed quick to grasp what was said to him. There was also a perceptible affective change; he was cooperative and grateful, rather than sullen and capricious.

Electroencephalograms (Dr. P. F. A. Hoefer) now showed a definite decrease in the number of abnormal complexes, which were clearly brought out only by

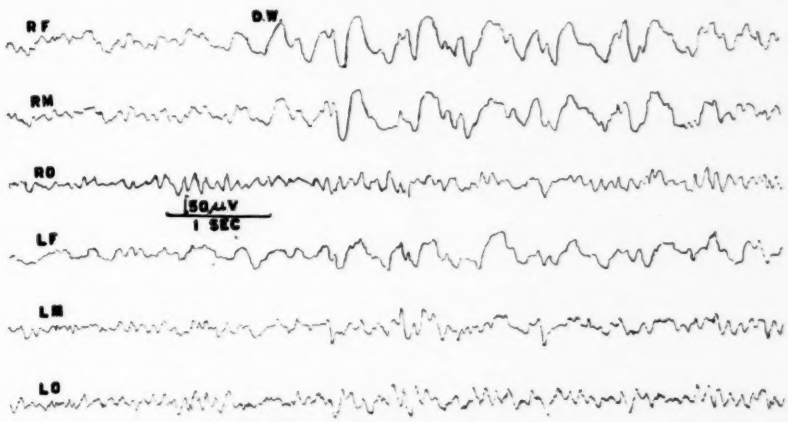

Fig. 2.—Electroencephalogram of D. W. (case 2) taken at a time when both the attacks and the dulness were well controlled by medication. In this figure and in the accompanying figures, *R F* indicates right frontal lead; *L F*, left frontal; *R M*, right motor; *L M*, left motor; *R O*, right occipital, and *L O*, left occipital. Note the similarity of the abnormality to that seen in figure 1. (Permission of Dr. P. F. A. Hoefer.)

hyperventilation (fig. 2). The improvement has continued progressively since this examination.

The dulness and mental confusion of which this patient complained could scarcely have been due entirely to the moderate dose of phenobarbital which he was taking. The reasons for believing that his retardation was due to a physiologic disturbance are three: the improvement under medication, the association of the periods of dulness with psychomotor phenomena of more familiar type and the correlative improvement in the electroencephalographic record.

Case 3.—John O'D., a telegraph operator aged 31, was first seen Dec. 8, 1938, having been referred by Dr. Walter Davies, of Somerville, Mass. Five years before he had a convulsion with unconsciousness, lasting thirty-five minutes. He then was free of attacks until 1938, when he had two. All of the attacks have come at night, and it is possible that more have occurred without being recognized. He thought the attacks were particularly prone to occur if he had been excited or worried.

In addition to the major attacks, according to his wife, he had more frequent minor attacks of which he was unaware. He was merely dazed and made purposeless movements with his hands.

Aside from these obvious attacks there were long periods, from several hours to a day or two, in which he was unable to concentrate or do his work at full efficiency. It was difficult to get a precise idea of how frequently these occurred, but the condition was definite and annoying to him.

He had received no medication.

The patient was alert, intelligent, cooperative and a good observer. Physical and neurologic examination revealed nothing of importance, except slight anisocoria.

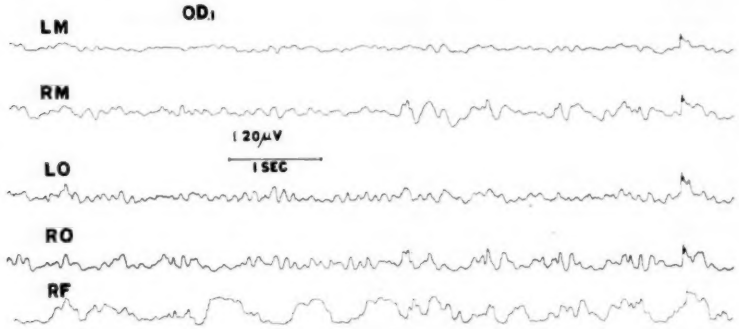

Fig. 3.—Electroencephalogram of J. O'D. (case 3) before medication. Note the long run of abnormal, slow, square-topped waves in the right frontal lead. (Permission of Dr. F. A. Gibbs.)

The usual laboratory studies, including roentgenograms of the skull and a lumbar puncture, revealed nothing abnormal.

Dr. Frederic Gibbs's report (Nov. 18, 1938) on the electroencephalogram (fig. 3) follows: "There is much slow activity, especially in the right motor and right occipital leads. No wave and spike (petit mal) and no fast (grand mal) activity was observed.

The patient was given phenobarbital, 0.1 Gm., every night. This medication made him feel sleepy nad uncomfortable during the daytime and produced no effect on his "absences." After a month of this treatment, the dose of phenobarbital was halved and 0.3 Gm. of dilantin sodium was added to it. Three months later, he reported that he was not disturbed by the medication and had had no further attacks of any kind. Further, the episodes of dulness and retardation had disappeared, and he felt general subjective improvement in alertness and energy. There was also improvement in the electroencephalographic record (fig. 4).

In this case (and in all of those which follow) the temporal relationship between electroencephalographic disturbances and the periodic

dulness was not demonstrated, but the patient showed periods of abnormally slow cortical rhythm. The effect of medication was definite and was noticed by his wife and the physician who saw him. He gave a fairly clear and characteristic account of his intellectual difficulties on direct questioning, and the diagnosis was made before the medication was begun.

Case 4.—W. C., aged 50, a tugboat mate, referred by Dr. L. E. Celentano, of New Haven, Conn., was first seen on Jan. 20, 1939. He gave a history of generalized convulsions beginning at the age of 23. At first they came at intervals of three to four years and then more frequently, until in 1938 he had four, which led to his retirement. The seizures lasted about twelve minutes; he would fall, have a convulsion and often injure himself. Usually he lost control of his bladder. On direct questioning, he gave no history of anything recognizable as petit mal or psychomotor seizures.

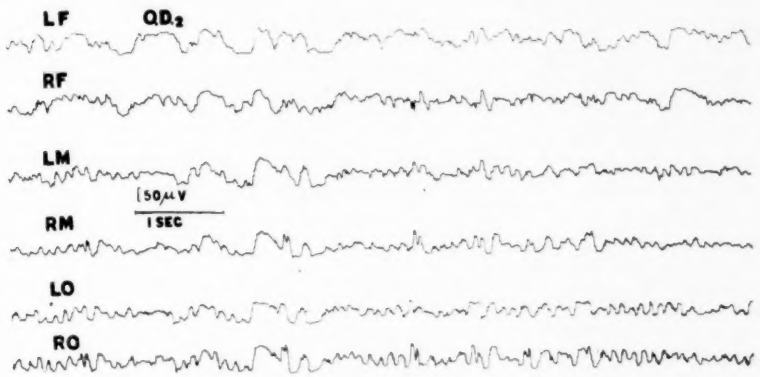

Fig. 4.—Electroencephalogram of J. O'D. (case 3) after convulsions and periods of dulness were relieved by medication. There is a slight, but definite, improvement in the record; abnormal stretches such as this were more difficult to find. (Permission of Dr. F. A. Gibbs.)

He had been known to have hypertension since 1924, but was otherwise healthy. Lumbar puncture (performed elsewhere) yielded normal results. He had been taking mebaral (n-methylethylphenylmalonyl carbamide), 0.3 Gm. daily, for two years, without improvement.

Examination showed a healthy, ruddy man, somewhat slow and anxious mentally. The blood pressure was 180 systolic and 96 diastolic; examination otherwise showed nothing remarkable. The blood count and urinalysis gave normal results.

Electroencephalographic studies (performed by Dr. F. A. Gibbs) showed the presence of both abnormally fast, high voltage waves, suggestive of grand mal activity, in the right frontal and right motor regions and groups of slow, 4 per second, square-topped complexes, such as are associated with psychomotor attacks, in all leads. The abnormal rhythms were not much increased by overventilation (fig. 5).

The patient was placed under treatment with a daily dose of 0.3 Gm. of dilantin sodium. This was well tolerated, and three weeks after his first visit an electro-

encephalogram, taken by Dr. Gibbs, showed a marked decrease in the rapid waves. The slow complexes of the psychomotor type persisted, however, and for this reason the dose of dilatin sodium was increased to 0.4 Gm. daily.

The patient when last seen on March 29, 1940, was strikingly more alert and cheerful. He had had no attacks and had returned to work, in charge of the deck crew.

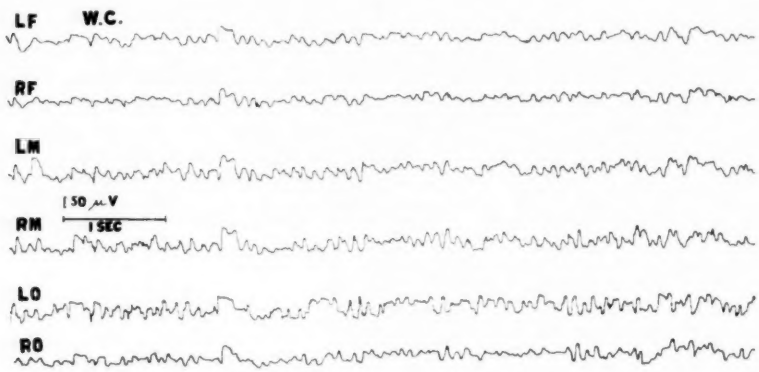

Fig. 5.—Electroencephalogram of W. C. (case 4) before treatment. Periods similar to the one shown were common. Note the recurrent square-topped complexes. (Permission of Dr. F. A. Gibbs.)

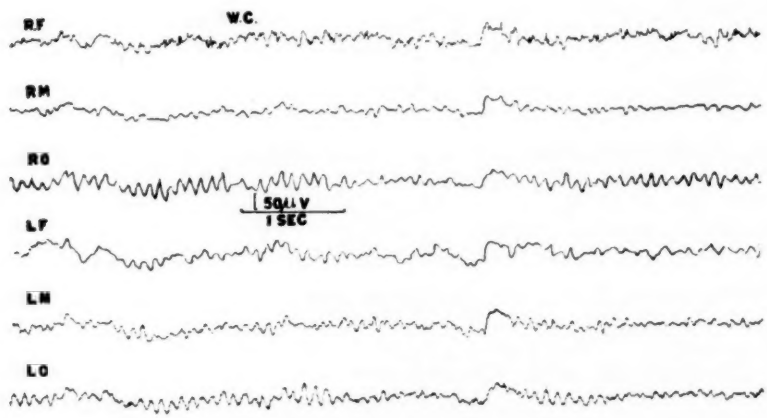

Fig. 6.—Electroencephalogram of W. C. (case 4) at his last visit, after the intellectual impairment had improved under medication and exercise. Such periods as the one shown were extremely rare. (Permission of Dr. P. F. A. Hoefer.)

The report of an electroencephalographic study (fig. 6), performed by Dr. Hoefer, follows:

"Monopolar records were obtained with six electrodes placed symmetrically with reference to the midline in the frontal, motor and occipital areas. The tracings were much more normal than those taken last year. Single, slow, large, square-

topped waves appeared occasionally in the left frontal area and rarely in the right frontal area, and, on one occasion, a single, generalized, square-topped wave was noted. Hyperventilation brought out a good deal of generalized activity of the same type, without increasing the amplitudes of the waves.

"The impression is that of subclinical psychomotor variant patterns."

The patient stated spontaneously that he "felt like a new man" since the last change. He said that in retrospect he could see that he had been hot tempered in his relations with the remainder of the crew and slow and stupid in his work—"in the mist," as he described it. The "mist" began to clear when he took dilantin and was at last completely dispelled when he resorted to out-of-door labor.

In this case, both abnormally rapid and abnormally slow cortical rhythms were observed, but the symptom of dulness persisted after the former had largely disappeared. Of particular interest were the partial response to medication and the further improvement with strenuous exercise. The characteristics of the symptoms were clearly recognized

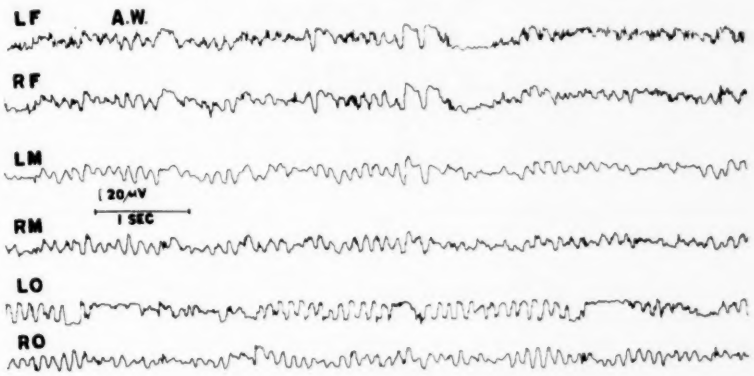

Fig. 7.—Electroencephalogram of A. W. (case 5) before treatment. Note the square-topped, slow waves in the frontal and motor leads. (Permission of Dr. P. F. A. Hoefer.)

and described by the patient in retrospect; they were not apparent to the examining physicians at the time the patient was first seen.

CASE 5.—A. W., an insurance clerk of 23, was referred by Dr. Thomas Carey, of Hartford, Conn. The patient considered himself in vigorous health until Oct. 15, 1938, when, after a period of nerve-racking work, he had an attack. It was ushered in by a compulsive memory of a story he had read; he had the sensation of smelling ozone, felt confused, could not talk and became unconscious for twenty minutes. During the following three months he had five similar attacks.

Examination, including lumbar puncture and roentgenographic studies of the skull, revealed nothing of importance. The electroencephalogram, taken by Dr. F. A. Gibbs, showed pathologic activity in the left temporal region, where high voltage, square-topped waves (at a rate of 2 to 4 per second) were easily produced by hyperventilation. A few occurred also at the rate of 6 per second (fig. 7).

The patient was treated with dilantin sodium in doses up to 0.4 Gm. per day. He thereafter had no more major attacks but continued to have minor ones daily or less often, which lasted a minute or less and were not accompanied by convulsive movements.

This situation continued with little change until August 1938, when, in addition to the "absences," he began to have intermittent difficulty in concentrating, for example, in reading a story to the end. This difficulty was somewhat variable, and at its worst would blend into a brief attack. Such periods and seizures have continued at intervals.

Throughout the first half of 1940 the patient's seizures were well controlled by medication, and he felt that his mind was clear. He began, however, to have brief episodes of aphasia. A small area of calcification was demonstrated in the left temporal lobe by roentgenogram. In December 1940 he began to have headaches, and a lumbar puncture showed increased intracranial pressure (210 mm.).

On Feb. 6, 1941 a craniotomy was performed, and subtotal removal of a large oligodendroglioma, which filled the left temporal lobe, was carried out. The patient was aphasic for about a month, but since then and up to the present (April 1, 1941) has been free of attacks and has felt normally alert and mentally active.

This case is of interest in several respects. The occurrence of dulness was spontaneously mentioned and described by the patient as a late symptom after the attacks of unconsciousness were largely controlled by medication. This was the only case in the series in which the attacks were caused by a definite expanding lesion. In view of this fact, their apparent relation to intellectual work and strain is of interest.

Case 6.—G. R., a widow of 46, referred by Dr. Leopold Stieglitz, of New York, began having definite short psychic equivalent attacks in 1917. At this time they occurred several months apart. They consisted of a lapse of consciousness, lasting a few moments without falling, during which she would often make an irrelevant remark. These attacks gradually increased in frequency in spite of treatment with phenobarbital, bromides, starvation, dehydration, various glandular extracts and psychoanalysis, until in January 1939 she had two attacks in which she completely lost control of herself and fell. At the time she came under our care, in February, she was having minor attacks about ten days apart.

Aside, however, from these definite attacks, she found herself much of the time in a state of extremely mild confusion. She found difficulty in attending to her social engagements and was aware of an intermittent lack of alertness. This was obvious to the examiner also on several occasions, when, without any interruption in the conversation or abnormal movements, she would return to some simple point which had already been discussed a few minutes before and was unable to follow straightforward instructions about hygiene and the dose of a drug. This confusion could scarcely have been due to her medication, which was moderate (phenobarbital 0.1 Gm. and bromides 0.9 Gm. daily). An electroencephalogram showed many slow, flat-topped waves suggestive of the type seen with psychomotor attacks.

Neurologic examinations and special studies of many kinds consistently yielded normal results.

She was given dilantin sodium, 0.3 Gm. daily, and had immediate relief not only from her psychic seizures but also from her dulness and confusion. She wrote at

the time: ". . . The absence of attacks is almost the lesser part of the miracle . . . By this I mean that I feel so different between attacks that I do not know myself . . ."

This degree of relief has unfortunately not been sustained. She has been unable to maintain a constant dosage of dilantin sodium. While she takes 0.3 Gm. daily she is entirely free from attacks and feels, as she says, transformed, but from time to time, especially just before her menstrual periods, she has severe headaches and dizziness, evidently resulting from her medication. When she omits or reduces the dose of dilantin, her attacks and her feeling of dulness and confusion recur. Since September 1939 she has had definite vasovagal attacks. She is an emotional and tense woman, with many psychologic problems aside from her attacks. It seems unlikely, however, that the former are an important cause of the latter, for she finds them distinctly easier to meet when the attacks are controlled by medication. On the other hand, attacks are usually precipitated by a heated argument or emotional scene.

In this case, the intellectual disturbances have a distinct affective cast, and the dulness is largely concealed by the emotional lability that accompanies them. It is possibly more than a coincidence that the patient is the only woman in the series. The electroencephalographic studies have been unsatisfactory. The effect of medication is striking, but relief from periods of dulness has been brief, owing to her intolerance to dilantin sodium. There is no mistaking the relationship between emotional disturbances of external origin and the onset of severe attacks.

CASE 7.—R. P., aged 17 was first referred by Dr. E. J. Sawyer, of Newton, Mass., on Oct. 13, 1938. For about five years he had been subject to "spells of blankness" lasting about five seconds, after which he would continue with what he had been doing. He could not say how often these occurred, but according to relatives they usually came several times a day. He had also had two major attacks with unconsciousness, convulsions and vomiting, one four years and another ten days ago.

He had undergone a thorough neurologic examination and the usual laboratory tests at another clinic one and a half years before, and no abnormalities had been found. He was then placed under treatment with phenobarbital, 0.03 Gm. daily, but gave it up spontaneously because he found that he had "mean spells" in which he would go into a tantrum or give surly answers to requests. He stated the belief, however, that he had fewer "blank spells."

Quite aside from these three types of attack, the patient was doing poorly at school and dropping behind his class.

Examination showed him to be tall and sturdy, but dull and apathetic. There were many points in the history in regard to which he was extremely vague. The results of neurologic examination were normal.

Electroencephalographic study (Dr. F. A. Gibbs) showed the presence of numerous irregular, slow complexes (fig. 8). He had had no externally apparent seizures, however. He was given dilantin sodium, 0.3 Gm. daily.

He was seen again on Feb. 21, 1939. He stated that he had had no further attacks of any sort and that his school average had risen progressively, so that his marks were mostly B's and A's. He seemed definitely more alert and responsive, told his story briskly, was appreciative of the relief he had received and in general appeared transformed.

The striking features of this case are, first, the lack of realization by the patient, his relatives or his physicians that his halting progress at school was connected with his attacks and, second, the objective evidence of relief afforded by the improvement in his school marks after treatment.

Of interest also is the manner in which medication with phenobarbital transformed his petit mal attacks into typical psychomotor tantrums. An increase in psychotic symptoms under treatment with phenobarbital has been noticed by other investigators.[15] In general, phenobarbital exerts its greatest effect in controlling abnormal fast activity, and one might conceive that the change in the nature of the attack coincided with the transformation of the spike and wave pattern to a slow wave rhythm.

Case 8.—A 20 year old white American youth was admitted to the Boston City Hospital in May 1939 with a history of grand mal attacks since the age of 3. From

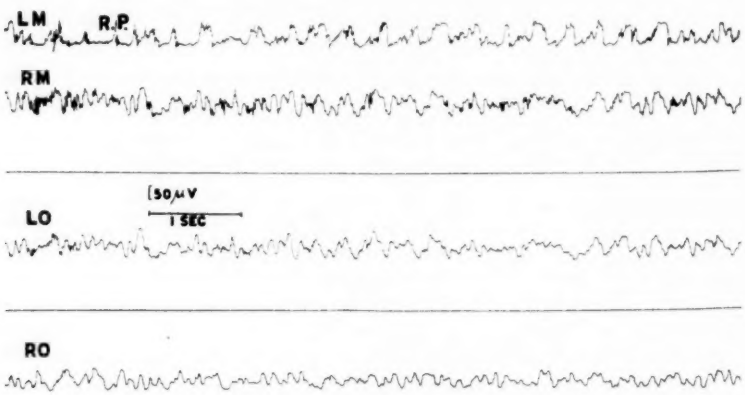

Fig. 8.—Electroencephalogram of R. P. (case 7) before medication. Notice the irregularity of the whole record, with some tendency to the formation of slow, square-topped waves. (Permission of Dr. F. A. Gibbs.)

the age of 3 to 13 the attacks had been infrequent and had occurred only at night, so that he had been able to continue at school to the seventh grade. Beginnnig at the age of 13 there was a sudden increase in the frequency of attacks, requiring his withdrawal from school. During the next seven years the attacks occurred at the rate of two to eight per day. These attacks were mild grand mal seizures with falling to the ground, loss of consciousness for one to two minutes and urinary incontinence. Treatment with ketogenic diet, bromides and phenobarbital, in a dose of 4½ grains (0.293 Gm.) per day, had not reduced the frequency of the attacks.

15. Roubinovitch, J., and Lauzier, J.: Contribution à l'étude comparée des divers traitements actuels de l'épilepsie, Ann. méd.-psychol. **1**:142-147, 1923. Foley, E. A.: Preliminary Report of Luminal Treatment in the Epileptic with Psychosis, Institution Quart., Springfield, Ill. **12**:107-108 (June 20) 1921. Lennox, W. G.: The Drug Therapy of Epilepsy, J. A. M. A. **114**:1347-1354 (April 6) 1940.

On physical examination the boy was dull and lethargic, with an acneform rash on the face. The speech was so dysarthric that it was understood with difficulty. The electroencephalographic record was abnormal, with many slow, high voltage waves. Psychometric examination was made by Dr. F. L. Wells. The mental age was 13 years, and the pattern of performance was indicative of functional loss.

Treatment with dilantin sodium was instituted on May 20, 1939, in a dose of 0.3 Gm. daily. There was an immediate decrease in the frequency of attacks, and after June 23, 1939, when the dose had been stabilized at 0.4 Gm. daily, there was complete cessation of attacks. In the fall of 1939, after seven years of complete invalidism, he returned to preparatory school and is doing excellent work in the classroom and participating in the athletic program of the school.

The chief points of interest in this case are the results of the psychometric examination and the evidence of intellectual improvement given by his school grades.

CASE 9.—A 15 year old white American boy was admitted to the Boston City Hospital in November 1937 with a history of petit mal seizures since the age of 9 and of grand mal seizures since the age of 12. The grand mal attacks occurred almost every day and the petit mal attacks several times daily. Routine studies, including spinal encephalographic tests, had been performed about one year previously at another hospital. Treatment with phenobarbital, bromides and a ketogenic diet had not been of any value, and the frequency of attacks had necessitated withdrawal from school two years previously. He had received some private tutoring at home but had made little progress. Management of the boy at home was becoming difficult. He was self centered, egotistic, overactive and disobedient.

Physical examination showed he was tall and well developed, with no significant abnormality. He was markedly overactive, both physically and mentally, with a fluctuant, excitable mood. Electroencephalographic studies showed slow, high voltage waves over both frontal lobes.

Treatment with dilantin sodium, 0.3 Gm. daily, was instituted in November 1937, with a decrease in the number of both the petit and the grand mal attacks. This dose was gradually increased to 0.5 Gm. daily, with reduction in the number of grand mal attacks to one every six months and in the petit mal attacks to one or two a week. Coincident with the reduction of the attacks there was a striking improvement in his behavior. He became more cheerful, lost most of his physical overactivity and became much better adjusted to his social environment. He remained at home for the next few months but entered preparatory school next fall, where he has been for the past two years. His school work has been of a high grade. He gets along well with his fellow students and instructors and takes an active part in the school athletcis, such as football.

The interparoxysmal state in this patient was dominated by an affective disorder, which tended to obscure the dulness. There can be no question, however, but that mental retardation took place also and was greatly affected by his medication.

CASE 10.—A 13 year old white American boy was first seen at the Boston City Hospital in August 1938 with a history of grand mal convulsive seizures since the age of 8. At the onset the attacks occurred at infrequent intervals, and he was able to stay in school for one year and finish the fourth grade of grammar

school. Frequency of seizures and inability to do the work necessitated his withdrawal from the fifth grade, at the age of 9. He stayed at home for the next one and a half years, having about one grand mal attack per day. An attempt was then made to return to school, but he had to withdraw again. There was no further education until nine months ago, when he was sent to a hospital school for retarded children. The patient had been studied recently in a hospital in another city, where all the routine examinations, including spinal encephalographic studies, had been performed. Treatment with ketogenic diet, bromides and phenobarbital had not reduced the frequency of the attacks.

On examination in August 1938 he appeared dull, with a bromide rash on the face, dysarthric speech and marked evidences of mental deterioration. The electroencephalographic tracing was one of the most abnormal that we have ever seen. The entire record consisted of high voltage waves at the rate of 3 to 5 per second from all portions of the cortex.

Treatment with dilantin sodium, in a dose of 0.3 Gm. per day, was instituted, with immediate reduction in the frequency of attacks and striking improvement in his mentality. The dysarthric speech disappeared, and the boy began to evidence an interest in reading and drawing. There were occasional seizures during the next few months while attempts were being made to establish the optimum dose of dilantin sodium. This was found to be 0.4 Gm. daily, and on this dose there have been no attacks for the past year. He returned to the public school, and in one year was promoted three times and completed three years' work.

The rapidity and extent of improvement in this case were striking. It is not clear, however, to what extent withdrawal of bromides was responsible. At one time, however, he had been forced to suspend his education on account of his interparoxysmal dulness, while at present he appears to be catching up with the average for his age.

COMMENT

The periods of dulness, apathy and mild affective disturbances of which the patients in the cases here reported—and many others—complain can scarcely be called "attacks." They are insidious in onset, last hours or days and are often only vaguely recognized by the patient or by those around him. There is seldom anything dramatic about them. They may constitute a serious problem, however, sometimes of as great importance as the actual convulsions or "absences" themselves.

As has already been remarked, this phenomenon can scarcely have escaped observation by others. It has doubtless often been included in the classification of psychomotor attacks or variants, but the usual definitions of the latter state would seem to exclude it. Spratling,[14] for example, defined psychic attacks as "a seizure of the mind, leaving the body as a rule, undisturbed; a temporary blank in the field of consciousness; a pathologic lapse in memory, varying from a second or two up to days and even weeks . . ." Elsewhere, he spoke of "processes of altered or lost consciousness." In most writings on the subject, psychomotor attacks are described in terms of pseudoaffective outbursts, brief

abnormal impulses, tantrums, etc., usually with some degree of amnesia. Such behavior disorders may, of course, coincide with periods of dulness, as in case 5.

Do similar periods of retardation and slight confusion, accompanied by definite alterations in the cerebral rhythm, occur in subjects who have no definite convulsive or petit mal attacks? We have no information on this point, but it seems reasonable to assume that they do. Jasper, Solomon and Bradley [6] found evidences of dysrhythmia in 59 per cent of a group of 71 children bearing the diagnosis of "psychopathic personality," and of course certain dysrhythmias have been described associated with various major psychoses. The impairment of mental activity displayed by the patients here reported on is, however, too slight and vague to be considered a definite psychosis, and it has apparently escaped systematic study. To what extent the electroencephalographic abnormalities and the dulness are interrelated must remain for further study to determine.

SUMMARY

A group of cases of "epilepsy" is reported in which periods of dulness, mental retardation, apathy and mild confusion occurred, lasting hours to days, in addition to definite attacks of typical grand mal, petit mal or psychomotor type.

Such periods are to be distinguished from neurosomatic deterioration, from the results of medication with sedatives, from the usual type of psychomotor attacks and from psychologic reactions to the disease by several criteria. First, careful amnestic study will reveal the intermittency of the symptom, its relation, if any, to sedative medication, its precise nature (usually without striking affective disturbance) and the patient's attitude toward it. Second, electroencephalographic records may demonstrate a correlation between the patient's reaction time, or his subjective awareness of retardation, and the presence of an abnormal rhythm. Third, the effect of a nonsedative anticonvulsant on the symptom may be determined.

PICK'S DISEASE

CLINICOPATHOLOGIC STUDY AND REPORT OF A CASE

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Neither the clinical nor the pathologic features of Pick's disease are uniform. As von Braunmühl [1] stated, "each case [of Pick's disease] suggests new problems." The clinical and pathologic pictures in the case here recorded are unique and are therefore of unusual interest.

REPORT OF CASE

History (Dr. Levitin).—G. O., aged 57, a white woman of Irish extraction, was admitted to the Psychiatric Institute of the University of Illinois on July 7, 1938. The history revealed that the patient's father died at the age of 76, about four years after he began to slip mentally. He became melancholy in the last nine months of his life and was childish and difficult to look after. One sister had epilepsy between the ages of 17 and 47. There were 11 siblings, of whom the patient was the eighth.

The patient was always a popular, attractive woman with "a lovely disposition." She dressed well and took an active interest in herself and in her family. She taught in the Chicago public schools and was thought to be a particularly skilful teacher of mathematics. She was married in 1906 to an alcohol addict, who died of pulmonary tuberculosis in 1923. Subsequent to his death the patient returned to her teaching and also held secretarial positions successfully.

About ten years previous to admission she began to worry excessively about her children, though before she had never been anxious about them. This anxiety increased progressively. Within the four or five years previous to admission she had three "fainting spells," at about yearly intervals. In 1935, while housecleaning, she fell 3 feet (90 cm.) to the floor. She did not become unconscious and suffered no residual pain or headache. About July 1937 she began to lose interest in her personal appearance and constantly wore the same clothing even after it became soiled. However, if clean clothes were laid out for her by some one else, she did not object to changing.

Read before the Chicago Neurological Society, Jan. 16, 1941.

From the Department of Neurology and Neurological Surgery and the Department of Psychiatry, University of Illinois College of Medicine.

1. von Braunmühl, A.: Zur Histopathologie der umschriebenen Grosshirnrindenatrophie (Picksche Krankheit), Virchows Arch. f. path. Anat. **270**:448, 1928.

Beginning in September 1937, the patient had more or less a reversal of the sleep cycle. She was drowsy and sleepy during the day and wakeful at night. She began annoying her children at night by going into their rooms to see if they were all right. At the same time she began to have visual hallucinations. She saw dogs and rats under her bed and observed eyes at the window. She stepped on imaginary bugs and picked them off the wall. After September 1937 she was unable to carry on an intelligent conversation. She would constantly reiterate the same stories and ask the same questions. When these repetitions were pointed out to her, she denied she was repeating herself.

During the first two months of 1938 she ate little, on some days nothing at all. In March 1938 she suddenly acquired an enormous appetite, which continued until shortly before her death. In May 1938 she began to soil and to wet herself. She always tried to get to the bathroom, but never got there quite on time.

The past medical history revealed little significant information. Birth and childhood were normal. She was said to have had few diseases in childhood. She did not have diphtheria, scarlet fever or influenza. Her adult life also revealed no evidence of illness. She went through the climacterium, at the age of 42, without changes in personality or behavior. All her teeth were extracted six years before admission, without sequelae.

Examination.—The results of physical and neurologic examinations were essentially normal. The patient was well developed and well nourished and appeared somewhat older than her age of 57; the temperature was normal; the blood pressure was 100 systolic and 70 diastolic; the pulse rate was 80 and the respiratory rate 20. There was a soft, blowing systolic murmur in the pulmonic area, which was not heard on subsequent examination. There was slight tenderness in the lower left quadrant of the abdomen, which also was not found later.

Examination of the blood, urine and spinal fluid all yielded findings within normal limits.

During the mental examination, performed a week after entrance, the patient spoke rapidly and almost constantly. She deviated constantly from the goal idea, usually referring to her family. Her answers were inconsistent, frequently even incoherent. She was partially oriented as to place and knew that she was in a hospital, but not that she was in the Psychiatric Institute. She knew the month, but was not sure whether the year was 1938 or 1939 and did not know the date or day of the week. Recent memory was completely lacking, and remote memory showed spottings of deficiency. Only very simple sums could be handled, and general information showed marked inadequacies.

On the basis of these findings and the history, a diagnosis of organic disease of the brain, probably presenile dementia, was made. The possibility of an intracranial neoplasm, however, was strongly considered, and an encephalogram was taken, which revealed large accumulations of air in the subarachnoid spaces over the right frontal pole. The ventricles were fairly well outlined and were not grossly displaced. There was some suggestion of dilatation of the anterior horns. The gyri were narrow and the sulci were widened throughout the cortex, especially at both frontal poles. Another encephalogram, taken eleven months later, showed greatly increased dilatation of the ventricles.

Course.—In November 1938 the patient grew increasingly worse. She did everything in a more ineffectual way, became more untidy in her appearance and once had an involuntary defecation on the floor. She failed to correct absurd questions; however, she remained oriented as to the month but was completely unaware of how long she had been in the hospital.

In November 1938 she was given a modified course of insulin treatments without induction of hypoglycemia, as suggested by Ziskind [2] for organic conditions of the brain. During the two months of this treatment the patient's family reported that she was much improved and much less anxious. However, any objective change noticeable in the ward was downward. In December 1938 she became completely disoriented as to time, place and person. In March 1939 she became more sloppy at the dinner table. Her underwear was often soiled with feces, and she would wash her hands and face with dirty water. She constantly drooled when she ate. She was found eating feces on several occasions. Distant memory was almost completely gone. She did not recognize objects but would occasionally pick up the correct object when directed. It is interesting to note that despite the apparently complete disorientation, at the time the patient was presented at a staff meeting in March 1939, she noticed sitting in the top of the balcony the physician who first saw her and said, "Oh, hello, Dr. ————," but at the same time failed to recognize the examiner who had been her physician for nine months.

The course remained progressively downhill. The patient died Sept. 7, 1939.

Special Observations.—In an effort to determine precisely which functions were still intact and which were deficient, the patient was subjected to a battery of performance and life situation tests.

Spatial Gnosis: To test spatial gnosis a large number of toothpicks was placed before the patient. A two dimensional form was constructed, as illustrated in figure 1. The patient was instructed to copy the examiner's form. The toothpicks were then again gathered into a pile, and the patient was asked to produce the previous form. (This experiment is adapted from Goldstein and Katz.)

It is interesting to note that in reproductions *1, 2, 9* and *15* of figure 1 the patient used additional pieces to give a more concrete form to the figure. In *3, 7* and *16* she used the correct number of pieces but rearranged them so that the resultant form had more meaning (i. e., more gestalt qualities). It is especially important to point out that *20,* seemingly the most difficult form—the one involving the greatest number of pieces—was handled by the patient with little distortion; the exact form was not reproduced after the removal of the original, but all the essential entities of the original were contained in her reproduction.

Letter and Word Gnosis: 1. Alphabet manipulation. An experiment was performed with 2 inch (5.1 cm.) high block letters, the letters of the alphabet being arranged in their correct order. The patient was asked to read the blocks. She responded: "C and D, F, G and 8 and 8 and L [she pointed to the I] and J; that is King [K] and that one L." She fingered the letters but did not read any more. The examiner pointed to each letter, starting with A. She read correctly each letter up to K and then said, "I don't know; no." After a pause she went on "L, and that is men [M]." She did not read the rest of the alphabet, even when letters were pointed to.

Some of the letters were pointed to, and she was asked what each was. She responded as follows: (N) "That's 'no'"; (M) "that's 'Mamie'"; (R) "that's 'hard'"; (W) "that's 'well'"; (P) "that's 'part'"; (S) "that's 'see'." To several other letters she responded, "I don't know."

It will be observed that in 5 instances she gave each letter a name of which that letter is the first. To one of these (M) she gave different names on two different

2. Ziskind, E.: Mechanism of Insulin Shock and Metrazol Therapy: Theoretical Considerations with Objective Evidence, Bull. Los Angeles Neurol. Soc. **5**:85, 1940.

occasions, but each beginning with the correct letter ("men" and "Mamie"). The letter R she called "hard," in which the sound "är" plays the maximum role. In this test it might seem on first glance that she was actually reading a more complex meaning into the letter than was actually present. However, a more consistent and

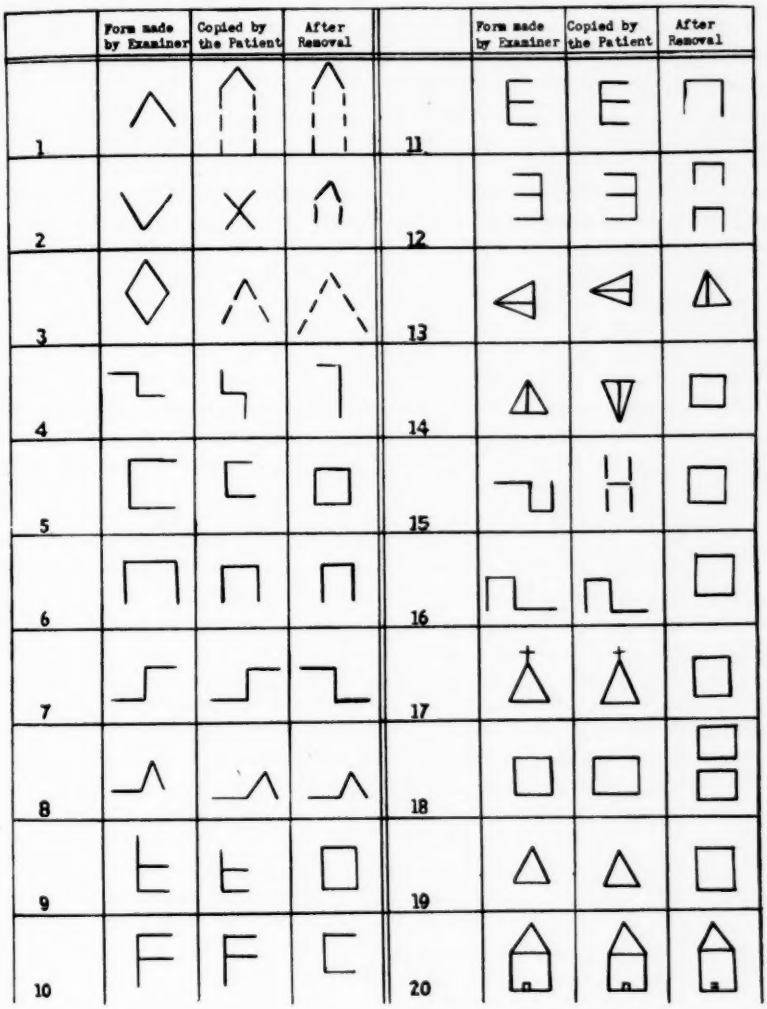

Fig. 1.—Forms used in tests of spatial gnosis and the reproductions by the patient (see text).

logical interpretation is that she was giving a simpler but more concrete meaning: For example, the concept "king" is more concrete, and yet simpler, than "K," "part" than "P," etc.

2. Writing. The patient was for several months able to write her own name, usually with two minor errors, "t" being substituted for "d" and "c" being present

twice instead of the correct once. Her children's last name she was invariably able to write, but the first names showed a constant stereotypy. When she was given her daughter's married name to write, she responded by writing the daughter's maiden name, thus obviously understanding what was meant, although not able to put down the correct name on paper. To all other words suggested, the patient responded with reiterative nonsense words, usually containing none of the essentials of the word called for.

3. Word gnosis. A sheet of 20 one syllable words was placed in front of the patient. When each word was pointed to separately, she read 5 words correctly, counting those she spelled. The same words were then written each on a separate single sheet in the same order. She was shown one word at a time. In this arrangement the patient read 13 words correctly, including those that she spelled. Apparently, the concept was clearer when she could focus her attention in a unified manner. The same procedure was later used with 15 two syllable words, and less than half as many two syllable as one syllable words were recognized.

In view of the possibility of fatigue playing a part in these results, fatigue tests were employed. The lists were reversed; different word series were tried, and several smaller series were also attempted. In all instances the results were essentially as have already been described.

Chronognosis[3]: 1. Reading time from a watch. The hands of a watch were set at various hours. She invariably read the full hour, never a part of it. The hour with which she responded was always that to which one of the hands of the watch was closest; e. g., at 4:50 she read the large hand only and said "10 o'clock" and at 12:40 she read the small hand only and said "1 o'clock."

2. Estimation of time. The patient was unable to tell which was more, two minutes or six seconds, three months or four weeks. Although she seemed to have no idea of the time of day, she asked for breakfast if it was not given to her on time.

While she was able to recognize in a very juvenile manner the method of telling time on a watch, her orientation for time was obviously poor. Her recognition of the hour on the watch would probably be more correctly classified as a spatial concept than as a temporal one.

Estimation of Magnitudes and Quantities: 1. Three glasses of water were placed in front of her, each containing a different amount of water. She was asked which glass contained the most, and the second most and the least water. This test was accurately handled on three occasions. In each instance the glasses had been rearranged spatially.

2. A heap of 50 pills was placed in front of her. Ten pills were separated from this heap. The patient was asked to separate the same number. She fingered the separated pills for a while and then made an attempt to count them. She said, "Nine." She was again asked to separate the same number from the big pile. She did and counted off 10 pills correctly. Asked how many she had, she responded, "Ten." Immediately thereafter she was asked to divide the heap of 50 pills into two equal parts. She counted off two piles of 10 and placed them just as she had when she was asked to separate 10. On three subsequent repetitions of this test the performance was identical.

Arithmognosis: 1. In early stages of her hospitalization the patient was able to handle very simple calculations. However, after six months she was no longer

3. The experiments on chronognosis and magnitudes are adapted from the article by Singer and Low (Acalculia [Henschen]: A Clinical Study, Arch. Neurol. & Psychiat. **29**:467 [March] 1933).

able to do any calculations. Block numerals were arranged in order from 1, 2, 3 to 9 and then 0. She read them off correctly except that after 9 she read "10." The numbers were jumbled, and she was asked to arrange them. The result was: 1 2 3 4 5 6 7 8 6 0. After she finished she went back and turned the 9 up correctly, saying, "Is that all right? That's a 9." The numbers were jumbled again, and she was asked to lay out number 2345. She picked up the numbers and again arranged them: 1 2 3 4 5 6 7 8 9 0. All subsequent attempts at complex numbers ended in the same result.

Performance in Spontaneous Life Situation Tests: Only a few of the many life situation observations which were recorded will be described:

1. The patient was asked to sit down; she did. Her shoes were slowly unlaced. She said, "Well, I put these on, yes." The lace was taken out of the shoe and thrown into the wastepaper basket, and her shoe was taken off and put aside. The patient said nothing relevant to the situation. She reached over for the shoe, took the lace out of the wastepaper basket, put on the shoe and laced it. She offered no resistance whatever and showed essentially no affect. She merely accepted the situation and continued her babbling, not even mentioning the frustration.

2. The patient's tray was always brought to her at the table. This time the meal was withheld. When the general call for a meal was given, she came and sat down at her usual table. After a few minutes she got up. She looked toward the food cart, then sat down again and said, "I always stay here." She remained sitting for several minutes. She said, "They ought to give me a lot of things." (What kind of things?) "I don't know. They give me a lot of things. I can't eat everything. They don't give me anything. No; I have to go out and get things." (What kind of things do you mean?) "I don't know." She made no attempt to get up and made no further comment for several minutes; however, she frequently looked in the direction of the food cart. She was finally told that she could go and get her tray. She said, "Yes, I'll go and get it." She got up at once, went to the food cart and said to the attendant: "They didn't give me anything."

In this situation she evidenced considerable bewilderment. However, there was some slight show of affect. She offered no solution to the problem herself but quickly adopted the solution offered to her by another. The concrete frustration was responded to merely by confusion, the patient being unable to think (abstractly) what (concrete) steps were necessary in order to solve her difficulty. However, when the solution was concretized by another, thus simplifying it, she quickly grasped the solution.

3. The examiner saw the patient trying to open the door. (She frequently begged to go home.) He gave her the key. She tried to use it, but failed. The examiner opened the door for her. She went out and stood in front of the elevator. (As is well known to all patients, this elevator does not run regularly.) After sixty seconds the patient rang both "up" and "down" buttons and then waited for two minutes. Then she looked at both stairways and finally walked to the next (third) floor. Here she again stood in front of the elevator for a minute looking up and down the shaft (this corridor is identical with that on her own ward floor). She looked through the ward door window and said, "I can't go here," returned to the stairway and walked to the fourth floor. Again she stood in front of the elevator, then tried the door to the occupational therapy room (in the same location as the ward door). She did not knock but continued to rattle the doorknob until an attendant opened the door. The patient went into the occupational therapy room,

sat down at the first table, picked up a piece of string and began to wind it into a ball. However, she failed to tie the ends of the string together, as the patients are instructed. When the examiner was discussing this failure with the occupational therapeutist, the patient said: "Well, I want to do everything." After a few minutes she said, "I want to go home." She was given the key to the door, and she succeeded in opening it. She went down to the third floor, looked up and down the elevator shaft and in the ward door and said, "I can't go in here; no." She then went down to her own ward and rattled the doorknob until admitted by a nurse. (She did not knock on the door.)

In this instance, again, she was able to understand the simpler concepts, but the more complex were too difficult for her. She understood that turning the doorknob was necessary in order to open the door, but not that the key was necessary. When she tried the upstairs door, she again concentrated on the simpler act of turning the knob. It never occurred to her to knock to attract attention. She grasped the simple fact that, since she had been on the elevator before, it would probably stop for her again. However, it took her sixty seconds to realize that the more complicated procedure of ringing the bell was necessary, and she apparently had no grasp of the still more complicated fact that the elevator did not run regularly.

Comment.—It became increasingly clear as this patient was studied that a great number of her difficulties could be accounted for on the basis of inability to handle concepts of any degree of complexity. Goldstein [4] expressed the belief that the defect is an inability to comprehend abstractions.

Her spatial orientation is likewise interpretable on the same terms. She appreciated the simple fact of being in a hospital, but comprehension of the more complex concept of the type of hospital and the name of the hospital was beyond her ability. Also, she was well aware she was in Chicago (she had lived there all her life), but she did not know in which part of the city she was. Separating the city into its component parts was too complex a procedure for her.

As has been already pointed out, her handling of letters, words and numbers also fits into the thesis that the more complex the concept the more difficulty the patient had with it. In the life situation observations also it was seen that the patient had little trouble with simple acts and behavior. When more complex ideation was necessary, particularly when a new situation presented itself, she was at a loss to solve the problem.

The question now arises whether we were justified in the diagnosis of Pick's disease on the basis of the available clinical data. Intracranial neoplasm, dementia paralytica and cerebral arteriosclerosis could all be quickly dismissed. In view of the encephalographic findings, the presence of air in the subarachnoid spaces over the frontal poles and the

4. Goldstein, K.: The Significance of the Frontal Lobes for Mental Performance, J. Neurol. & Psychiat. **17**:27, 1936.

suggestive dilatation of the anterior horns of the lateral ventricles, Pick's disease, in addition to Alzheimer's disease, had to be considered. The latter is a much more rapidly progressing affliction than Pick's disease; focal signs, convulsions and spasticity are more common. Disorientation is early and usually complete. Disturbances of speech are common, but the higher functions are not alone affected, as in Pick's disease, and memory defects are earlier and more complete. On the basis of one or two of these criteria, we could draw no definite conclusions, but on the basis of the clinical picture as a whole a diagnosis of Pick's disease was certainly suggested.

Fig. 2.—Cytoplasmic and fibrillary astrocytes from the temporal lobe. Their processes extend to the vessel walls, which they cover and separate from the parenchyma. Holzer stain (Warkany modification).

Pathologic Observations (Dr. Hassin).—Grossly the brain appeared small and weighed 960 Gm. Even with the pia-arachnoid attached, it exhibited atrophy of the frontal lobes, especially of their orbital areas, and to a lesser extent of the temporal lobes, with practically normal-appearing occipital lobes. The atrophy was more marked when the pia-arachnoid membrane was detached. The convolutions were narrow; the sulci were gaping, and the lateral ventricles were dilated. The meninges, basilar arteries and ependymal lining of the ventricles presented nothing pathologic.

Microscopic Observations.—The most striking features were present in sections which were stained by the method of Holzer (modified by Warkany). Enormous

proliferation of protoplasmic and fibrillary astrocytes was in evidence, especially in the frontal and temporal lobes of both sides. Figure 2 shows the mighty astrocytic processes extending to the adventitia of the blood vessels, separating them from the surrounding parenchyma. The astrocytes often formed foci, which, as figure 3 shows, appeared as dark islands. The islands of astrocytes gave the field a variegated appearance and were present throughout both the cortex and the subcortex. In the lamina zonalis, the subpial layer of the cortex, astrocytes were also numerous and were intermingled with fibrillary glia. This glia tissue appeared as a dense feltwork (fig. 4 *A*), which did not invade the pia mater and was conspicuous in the form of rings around the blood vessels. Some regions of the temporal lobe presented a rather curious accumulation of amyloid bodies (fig. 5). Their numbers were so immense that they even overshadowed the feltwork of the subpial layer.

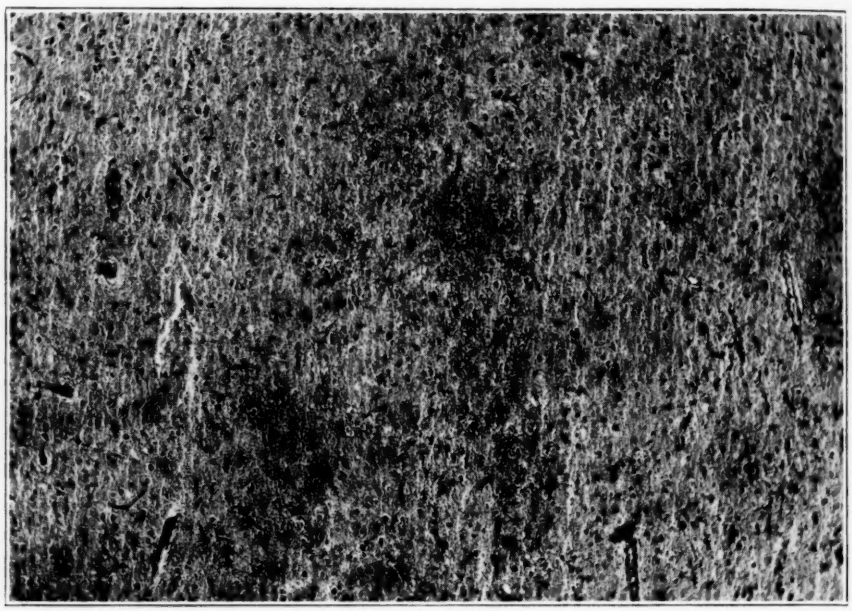

Fig. 3.—Frontal lobe (orbital gyrus). The dark spots are foci of astrocytes described in the test. Holzer stain (Warkany modification).

In general, the glial changes in the temporal lobe and elsewhere were marked in all the cortical layers, probably more in the deeper ones and gradually decreasing in the direction of the pia. In the white substance the glia appeared as an extensive scar, even in regions in which the parenchymatous changes were slight or absent (cornu ammonis, cerebellum, medulla, substantia nigra and spinal cord). Figure 6 shows such glial changes (*A*) in the cerebellum and (*B*) in the corpus striatum, and figure 7, those in the spinal cord. In the cerebellum the dense bands of glia fibrils enveloped even the smallest blood vessels and contained no nuclei or other cell bodies. In the corpus striatum (fig. 6 *B*) the glia fibrils appeared as parallel bands, which in some areas reproduced the course of destroyed nerve fibers and exhibited isomorphous gliosis, while the subependymal area of the optic thalamus

Fig. 4.—*A*, dense glial feltwork in the upper layer of the lamina zonalis and around patent blood vessels.

B, Sclerotic (parenchymatous) atrophy of the cerebellum. The histologic picture is similar to that shown in *A*.

was represented by an enormously thickened layer of glia fibers mixed with oligodendrocytes. Foci of astrocytes did not occur in this area, but were present in the various thalamic nuclei, in which the ganglion cells were degenerated. In the spinal cord dense fibrillary glia occupied the anterior (fig. 7 *B*) and the basal parts of the posterior cornua, obscuring some ganglion cells, which for the most part were preserved or had undergone only mild changes. Some were slightly swollen; others were homogenous or exhibited chromatolysis, and very few were vacuolated or broken up. From the glial feltwork of the anterior horns (fig. 7 *B*) long glia fibers emanated, running in parallel formation and extending to the white substance of the ventrolateral columns, where they seemed to surround each nerve fiber. Sometimes they were so dense that they obscured the axons and the

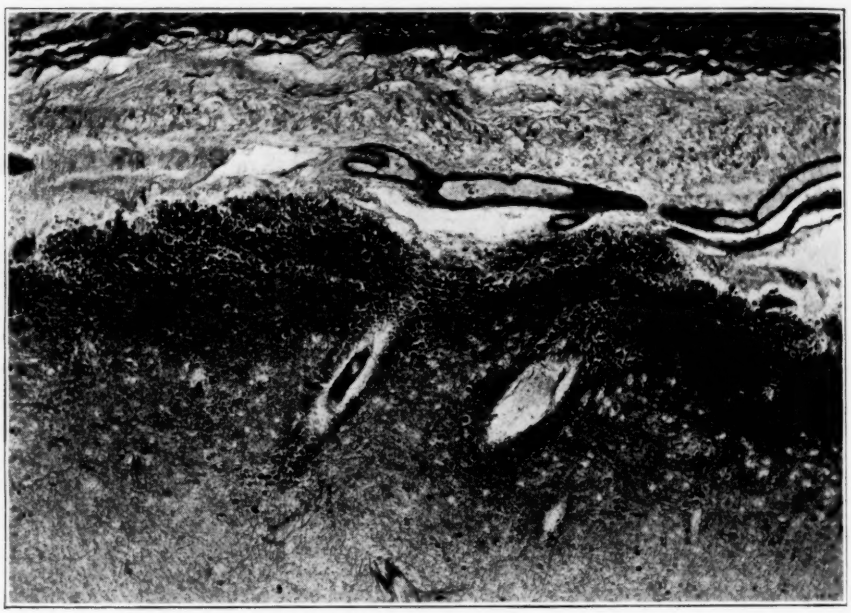

Fig. 5.—The feltwork of the subpial layer is crowded with amyloid bodies, which are also gathered around the patent blood vessels. Holzer stain (Warkany modification).

myelin. When cut transversely they appeared as numerous dots or gathered in dense masses. Similar glial changes were present in the medulla oblongata, especially in the olivary bodies. These were surrounded by a feltwork of thin glia fibrils, which contained oligodendrocytes but no astrocytes. No particular changes were present in the ganglion cells of the olives. The rest of the medulla oblongata was practically normal, except the nuclei of the ninth and tenth nerves, in which the changes were similar to those in the olivary bodies. It should be emphasized that in a normal medulla the olivary bodies, when stained by the method of Holzer, appear darker than the neighboring areas, but without changes in the glia, as described here.

Comparatively mild were the changes in the pons, cerebellum and central convolutions, anterior and posterior, where islands of astrocytes were encountered only occasionally and the cortical cell layers were distinct. Even in the atrophied areas, the temporal, for instance, the lamellation was for the most part preserved, especially in the upper two layers and partly in the third, where, as figure 8 *A* shows, outfall of ganglion cells had resulted in formation of areas of devastation

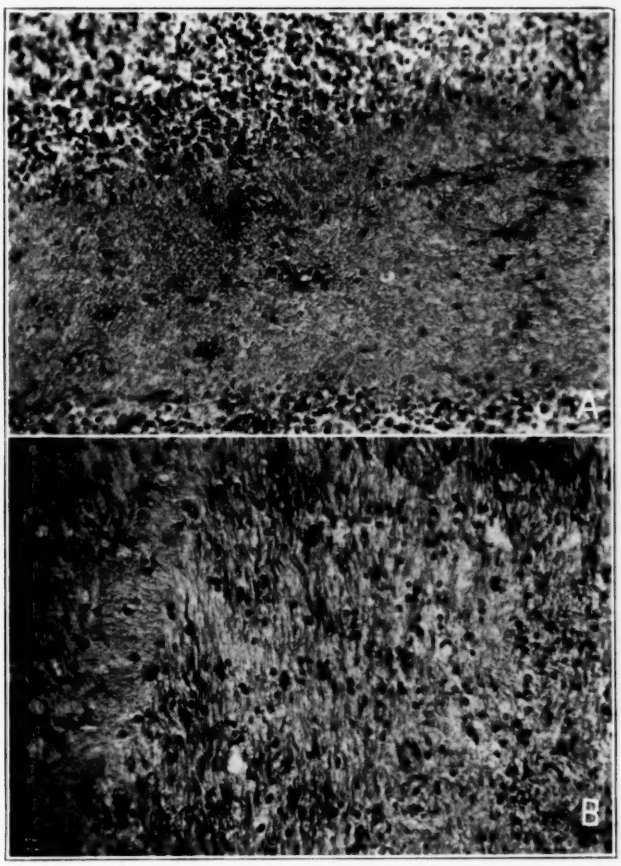

Fig. 6.—*A*, the white matter (core) of a cerebellar folium is transformed into a glial tissue scar containing a few astrocytes.

B, corpus striatum. Isomorphous gliosis (bundles of parallel-running glia fibers) appears in the center of the photomicrograph. Holzer stain.

(barren, avascular or acellular areas). In these areas, and also in their neighborhood (*a a*) and in the subcortex, there was an enormous astrocytic proliferation. This was particularly true of the subcortex (fig. 8 *B*), which appeared extremely crowded with astrocytes, glia and nerve fibers. Astrocytic proliferation was

combined with practically normal ganglion cells and nerve fibers, which were obscured by the abnormal overgrowth of the glia elements.

The ganglion cells occasionally appeared homogeneous and devoid of processes, or were present as cell shadows, and seldom exhibited phenomena of satellitosis and neuronophagia. The expanded or swollen ganglion cells considered by some authors (Schneider [5]) as typical of Pick's disease, especially in its early stages, were absent. There were no changes in the neurofibrils, no plaques (*Drusen*) and no inclusions (spherules of Alzheimer, or an excessive amount of lipoids), and lipoids were not present in the adventitial spaces of the blood vessels or capillaries, where

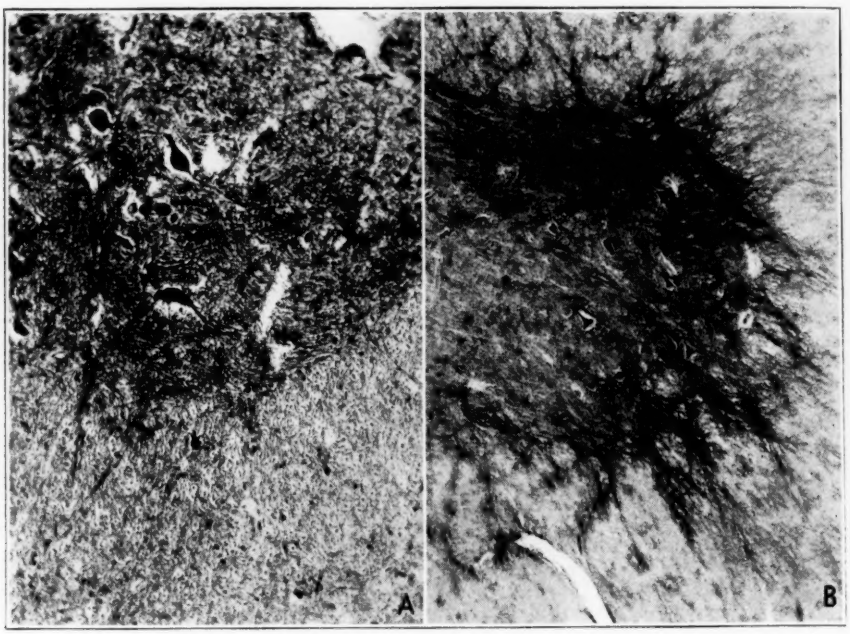

Fig. 7.—*A*, ganglion cells and nerve fibers in an anterior horn of the upper cervical portion of the cord in a case of Pick's disease. Bielschowsky stain.

B, same horn as that shown in *A* stained by Holzer's method. There is an abundance of fibrillary glia, especially in the marginal areas, with digit-like processes and numerous ganglion cells.

green pigment granules were encountered in specimens stained with toluidine blue and occasional dark red granules were seen in specimens stained with turnbull blue.

The nerve fibers in the cortex—tangential and radiary—were sparse or absent, but were abundant in the subcortex, even in the areas which were rich in glia tissue. In specimens stained by Weil's method for myelin, the nerve fibers were

5. Schneider, C.: Ueber Picksche Krankheit, Arch. f. Psychiat. **65**:230, 1927; Monatschr. f. Psychiat. u. Neurol. **65**:230, 1927.

thinned and sparse and separated from one another by a poorly defined substance, which, when stained by other methods, was found to consist of minute fragments of myelin mixed with glia nuclei and glia fibrils. Grossly, the subcortex, when stained by Weil's method, was paler than normal (fig. 9), but by no means was it as pale as similarly stained degenerated areas in cases of Schilder's disease or multiple sclerosis. The demyelination of the subcortex in the frontal lobes (fig. 9, F_1, F_2, F_3), for instance, seemed to be rather mild in view of the vast involvement of the glia, while in the temporal gyri, which also exhibited extensive gliosis, demyelination was absent altogether (fig. 9, *T*). It should be emphasized that neither the nerve fibers nor the ganglion cells in the case under discussion presented

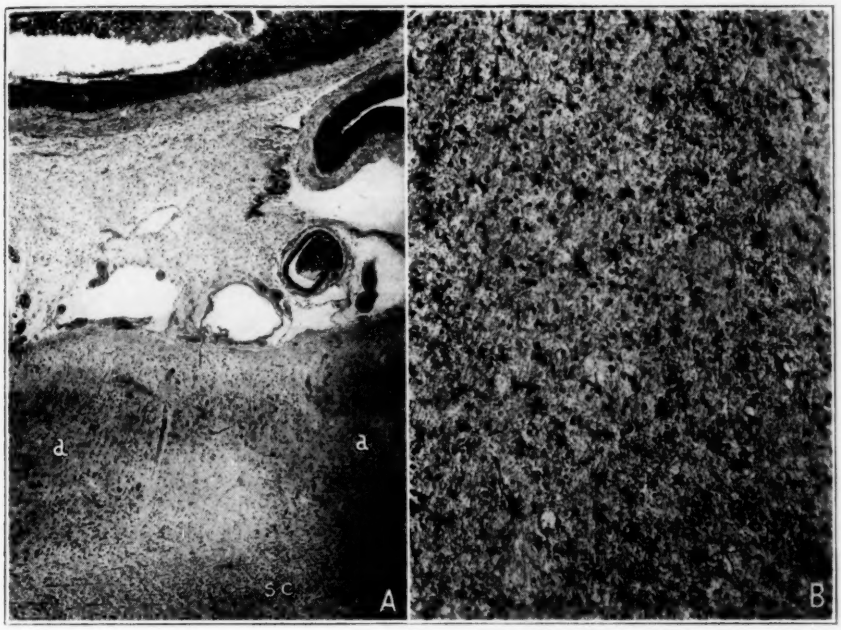

Fig. 8.—*A*, an extensive area of devastation in the temporal lobe, bordered by similar smaller areas (*a a*) and involving the lower cortical layers (from the third to the subcortex). The subcortex (*s c*) and the subarachnoid space are markedly cellular.

B, diffuse gliosis of the subcortex described in the text.

as striking changes as did the glia. The immense glial proliferation with formation of astrocytes was decidedly out of proportion to the extent of the parenchymatous changes, which, as has been stated, were relatively mild.

The blood vessels, as figure 2 shows, appeared patent, were not infiltrated with hematogenous elements and generally were normal. The endothelial cells of the capillaries appeared occasionally hypertrophied and proliferated. The smaller blood vessels often were shrunken and collapsed or had dropped out, leaving empty spaces surrounded by rings of glia fibers (fig. 4 *A*).

The subarachnoid space (fig. 8*A*) was distended, and the pia-arachnoid was hyperplastic. It contained lymphocytes, polyblasts, foci of mesothelial cells and histiocytes filled with lymphocytes, granules of blue pigment, gitter cells and fibroblasts, some of which were large and vacuolated.

Summary: There were excessive proliferation of cytoplasmic and fibrillary astrocytes throughout the cerebral subcortex and brain stem; formation of minute

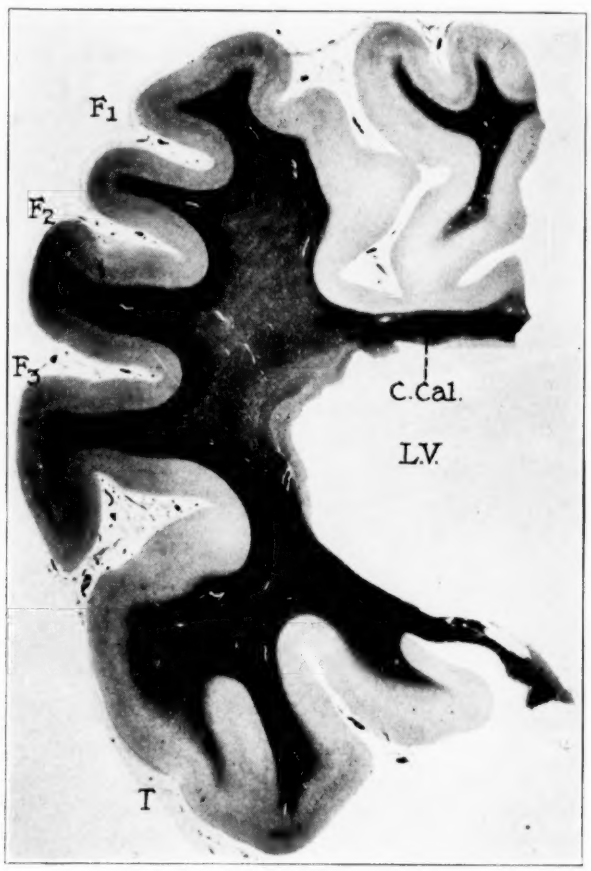

Fig. 9.—Coronal section through the rostrum of the corpus callosum. The U fibers are well stained; the subcortex of the frontal convolutions is paler than that of the temporal lobe. The lateral ventricle (*L. V.*) is dilated, and the corpus callosum (*C. Cal.*) as well as the frontal (F_1, F_2 and F_3) and temporal convolutions (*T*) are atrophied. Weil stain.

islands of astrocytes and extensive glial tissue scars, especially in the subcortex; relatively mild changes in the parenchyma (the ganglion cells and nerve fibers), and normal blood vessels.

Comment.—The changes in the central nervous system described in this case were not confined to specific lobes and were not "circumscribed," as Pick [6] emphasized on the basis of gross pathologic observations only, but were diffuse. The changes not only extended throughout the cerebral hemispheres but were marked in the pons, cerebellum, medulla and spinal cord (at least the cervical portion). For the most part they appeared, as has been stated, in the form of small islands of astrocytes, well shown in figure 3. They were mentioned by Ferraro and Jervis,[7] who spoke of small areas of sclerosis irregularly distributed in the gray and white matter. Wherever they were present in this case they exhibited a remarkable contrast between the mildness of the parenchymatous and the severity of the glial changes.

In my opinion, too much emphasis has been placed in Pick's disease on the condition of the ganglion cells, the lamellation of the cortex and the size of the gyri, but relatively little attention has been centered on the condition of the white substance of the brain, the cerebellum or the spinal cord. The latest authors (Altman,[8] von Braunmühl,[1] Korbsch,[9] Kufs,[10] Lemke [11] and Malamud and Boyd [12] have mentioned the diffuse character of the glial changes with the involvement of the subcortex and corpus striatum, while von Braunmühl and van Husen [13] noted the disproportion in the severity of the changes in the gray and white substances.

In the present case practically every portion of the central nervous system was affected—the neocerebrum and the paleocerebrum, the neocerebellum and the paleocerebellum, the medulla oblongata and the spinal

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6. Pick, A.: (*a*) Ueber die Beziehungen der senilen Hirnatrophie zur Aphasie, Prag. med. Wchnschr. **17**:165, 1892; (*b*) Senile Hirnatrophie als Grundlage von Herderscheinungen, Wien. klin. Wchnschr. **14**:403, 1901; (*c*) Zur Symptomatologie der linksseitigen Schläfenlappenatrophie, Arch. f. Psychiat. **16**:379, 1904; (*d*) Ueber einen weiteren Symptomenkomplex im Rahmen der Dementia senilis, bedingt durch umschriebene stärkere Hirnatrophie (gemischte Apraxie), Monatschr. f. Psychiat. u. Neurol. **19**:97, 1906.

7. Ferraro, A., and Jervis, G. A.: Pick's Disease: Clinicopathologic Study, with Report of Two Cases, Arch. Neurol. & Psychiat. **36**:739 (Oct.) 1936.

8. Altman, E.: Ueber die umschriebene Gehirnatrophie des späteren Alters, Ztschr. f. d. ges. Neurol. u. Psychiat. **83**:610, 1923.

9. Korbsch, H.: Picksche und Huntingtonsche Krankheit bei Geschwistern, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:326, 1933.

10. Kufs, H.: Beitrag zur Histopathologie der Pickschen umschriebenen Grosshirnrindenatrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:786, 1927.

11. Lemke, R.: Ein Beitrag zum Krankheitsbild der Pickschen Atrophie, Arch. f. Psychiat. **101**:623, 1934.

12. Malamud, N., and Boyd, D. A., Jr.: Pick's Disease with Atrophy of the Temporal Lobes, Arch. Neurol. & Psychiat. **43**:210 (Feb.) 1940.

13. van Husen, T.: Ueber einen Fall von Pickscher Krankheit, Allg. Ztschr. f. Psychiat. **101**:381, 1934.

cord, the gray and the white substance; some parts were affected more and others less, but the lesions extended from the frontal to the occipital pole. In all the aforementioned areas the changes in the glia dominated the field. They were typical of the terminal stage of nerve degeneration, but did not exhibit its intermediary phases, which are observed in multiple sclerosis, amyotrophic lateral sclerosis, subacute combined degeneration of the cord, Friedreich's ataxia and similar conditions. There were no fat granule bodies (gitter cells), which were only occasionally observed in the adventitial spaces of the capillaries and blood vessels. Yet, in spite of such advanced changes in the glia, parenchymatous changes, in the ganglion cells and nerve fibers, were relatively mild or absent. For instance, there were hardly any parenchymatous changes in the cerebellum, the cornu ammonis, the spinal cord and the medulla oblongata, though progressive glial changes in these areas were immense. This can be well seen by comparing the pictures in figure 7. In *A* is shown a ventral horn in the upper portions of the spinal cord which is rich in ganglion cells and nerve fibers. In *B* the same field, stained by the method of Holzer, shows many bundles of glia fibers following the course of the ventral nerve root fibers. When such sections were stained by the method of Weil, they exhibited no demyelination. Demyelination undoubtedly would have occurred if the glial overgrowth had been a manifestation of destruction of the parenchyma, that is, if the changes in the glia had paralleled those in the ganglion cells or nerve fibers, as has been assumed by Onari and Spatz [14] and others. Nor was demyelination present in the medulla oblongata, where glial proliferation was immense. Only in the atrophied frontal lobes (fig. 9) did the subcortex exhibit paleness, in striking contrast to the color of the U fibers. Though Lemke [11] affirmed that the pallor of the frontal and temporal lobes may be diffuse and intense so as to resemble foci of multiple sclerosis, demyelination is rare in Pick's disease, according to Urechia [15] and Onari and Spatz.[14] One, therefore, must assume that in Pick's disease the glia does not replace a destroyed parenchyma (this, of course, may exhibit more advanced changes than those described in the present case) but that it represents an independent overgrowth, merely enveloping the ganglion cells and the nerve fibers.

The widespread and intensive glial overgrowth is morphologically analogous to that which is seen in sclerotic (parenchymatous) atrophy

14. Onari, K., and Spatz, H.: Anatomische Beiträge zur Lehre von der Pickschen umschriebenen Grosshirnrindenatrophie (Picksche Krankheit), Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:470, 1926.

15. Urechia, C. J.: Contribution à l'étude de la maladie de Pick, Encéphale **25**:728, 1930.

of the cerebellum.[16] In this condition there is widespread destruction of the ganglion cells of the cerebellar cortex with extensive glial scar formation (fig. 4 *B*). In the case under discussion the ganglion cells of the cerebellum were not affected, and though the cores of some folia were "sclerosed" (fig. 4 *A*), they contained a wealth of preserved nerve fibers. Verhaart,[17] van Husen,[13] Giljarowsky[18] and others, however, observed involvement of the cerebellar ganglion cells in Pick's disease, but unfortunately this was not illustrated or was insufficiently described. Only Verhaart gave a picture of the cerebellar changes, which are strikingly similar to those of sclerotic atrophy of the cerebellum. The latter thus can occur in Pick's disease, but it is not a part of the pathologic picture. It is noteworthy that the sclerotic type of cerebellar atrophy has not been observed in association with other cerebral atrophies which occur in certain forms of dementia paralytica, amaurotic family idiocy, Alzheimer's disease, Huntington's chorea and senile dementia. It is a typical feature only in crossed atrophy of the cerebellum,[19] in which it is associated with contralateral atrophy of the cerebral hemisphere and in which the changes are local, and not diffuse, as they are in Pick's disease. For this reason, crossed atrophy of the cerebellum, sclerotic (parenchymatous) atrophy of the cerebellum and Pick's disease, though possessing some features in common, are to be considered distinct pathologic entities.

The cause of the glial overgrowth and of the parenchymatous changes in Pick's disease is not known. The involutional theory (Pick[6a] and Kufs[10]) that it is a form of senile or presenile dementia, Reich's[20] theory of involvement of the association tracts with the complete or relative sparing of the cortex, the "philogenetic" speculations of Gans[21] (phylogenetically young portions of the brain are preferably affected), the heredodegenerative hypotheses (certain factors, according to Gans[21] and Onari and Spatz,[14] attack portions of the brain which possess a highly differentiated function and for this reason cannot resist unfavorable influences), the vascular theory—all are mere hypotheses and explain

16. Hassin, G. B.: Sclerotic Atrophy of the Cerebellum, Arch. Neurol. & Psychiat. **31**:1205 (June) 1934.

17. Verhaart, W. J. C.: Pick's Disease, Nederl. tijdschr. v. geneesk. **74**:5586, 1930.

18. Giljarowsky, W.: Zur Pathologie der Rückentwicklungsprozesse, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:509, 1932.

19. Hassin, G. B.: Crossed Atrophy of the Cerebellum, Arch. Neurol. & Psychiat. **33**:917 (May) 1935.

20. Reich, F.: Zur Pathogenese der circumscripten resp. systemartigen Hirnatrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:803, 1927.

21. Gans, A.: Betrachtungen über Art und Ausbreitung des krankhaften Prozesses in einem Fall von Pickscher Atrophie des Stirnhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **80**:10, 1923.

nothing. It is true that disseminated lesions may, as has been shown by Neubürger,[22] result from vascular disturbances (in arteriosclerosis of the brain, for instance) and that "senile," diffuse or island-like devastations may occur in the cortex from involvement of the short cortical blood vessels (Brinkman[23]), but the vascular theory cannot explain the practically universal and the more intense involvement of the glia. With vascular lesions the parenchyma is more affected than the glia and foci of softening are associated with marked mesodermal reaction, while in Pick's disease the foci are those of sclerosis and the reaction is glial.

Intoxication probably explains the changes in Pick's disease better than any other hypothesis. Intoxication was the unquestionable cause of the changes which Weil and Liebert[24] produced experimentally in animals by injections of metrazol and which they observed in human beings who had been treated with repeated injections of this substance. In 2 of the 6 cases in which metrazol treatment had been used (for from two to six months) these authors observed no parenchymatous changes but, instead, marked hypertrophy and hyperplasia of astrocytes and, to a lesser extent, of the microglia, which was inconspicuous also in the present case. Injections of metrazol, therefore, may produce both extensive glial reaction and mild parenchymatous changes. The analogy between the changes produced by injections of metrazol over long periods (in 1 case of Weil and Liebert as many as fifty-three injections of metrazol were given) and those seen in Pick's disease is so great as to justify the assumption that the cause of Pick's disease is an intoxication. It affects both the parenchyma and the glia, producing an extensive reaction in the latter.

CONCLUSIONS

A case of Pick's disease has been diagnosed on the basis of psychologic examination supplemented by encephalographic observations.

On the basis of the tests administered it is concluded that a unitary explanation of the available psychologic data is indicated, namely, that inability of the patient to understand a concept is in inverse proportion to the complexity of the concept.

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22. Neubürger, K.: Ueber streifenförmige Erkrankungen der Grosshirnrinde bei Arteriosklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:452, 1926.

23. Brinkman, F.: Ueber flächenhafte Rindenerweichungen bei Arteriosklerose der kleinen Rindengefässe, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:182, 1926.

24. Weil, A., and Liebert, E.: (*a*) Neuropathologic Study of Six Cases of Psychoses in Which Metrazol Was Used, Arch. Neurol. & Psychiat. **44**:1031 (Nov.) 1940. (*b*) Liebert, E., and Weil, A.: Histopathologic Changes in Brain Following Experimental Injections of Metrazol, ibid. **42**:690 (Oct.) 1939.

Progressively developing dementia without focal signs, such as aphasia or apraxia, may be the sole manifestation of this morbid condition.

The histologic changes are not circumscribed but are diffuse and involve both the parenchyma and the white substance as well as the glia of the entire brain, including the basal ganglia, the cerebellum, the pons and the medulla and probably the entire spinal cord.

The glial changes overshadow those of the parenchyma, where they are generally mild and may even be absent.

The cerebral changes are in some features analogous to those of sclerotic (parenchymatous) atrophy of the cerebellum and may be combined with it.

The changes bear also a great resemblance to those occurring as the result of prolonged administration of metrazol and are probably due to a chronic intoxication.

DISCUSSION

Dr. Arthur Weil, Chicago: It has always been emphasized in the literature that in Pick's disease the neurons of the upper cortical laminas are more severely diseased than the lower, and are sometimes exclusively involved. Did the authors not notice any of those changes described as balloon-like swelling or complete atrophy of neurons with diminution in their number?

It is true that after experimental injections of metrazol in rabbits there are remarkable hyperplasia and hypertrophy of the astroglia. However, the microglia is stimulated too, and giant rod cells may be seen in the more advanced stages. In 1 case of Pick's disease which I had the opportunity to study, there were both marked disease of the neurons with demyelination of the white matter and marked hyperplasia of the astroglia and the microglia.

Dr. George B. Hassin, Chicago: Too much stress has been laid on the condition of the ganglion cells of the cortical layers in Pick's disease. Some investigators have emphasized the involvement of the upper layers, and others, that of the lower layers or of both upper and lower layers. Nor is the swelling of ganglion cells described by Schneider of significance. It is apt to occur in cases of the "acute," or "stormy," form of the disease, but it is by no means pathognomonic and was not present in our case. Neither is the condition of the microglia in this disease of any significance, as microgliocytes occur wherever there is trouble in the central nervous system, being its scavengers, as are the reticuloendothelial cells elsewhere. The outstanding and unique feature in Pick's disease is the discrepancy between the relatively mild parenchymatous changes and the severe neuroglial changes. I have not encountered it in any other neuropathologic condition. Only Weil and Liebert have emphasized that in the brains of rabbits and human beings metrazol caused marked hypertrophy and hyperplasia of the astroglia associated with mild changes in the parenchyma and that, except in the cases of 2 of 6 patients studied, they found no marked pathologic changes in the neurons.

THE ELECTROENCEPHALOGRAM OF CHILDREN WITH FOCAL CONVULSIVE SEIZURES

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NEW YORK

Convulsive attacks which are limited to one half of the body or to a single limb have always been of interest to neurologists, who hope in each case that a focal cortical lesion may be found to explain the occurrence of seizures and that removal of the lesion may effect a cure. In the majority of cases this hope is not realized, for all too often neither operation nor necropsy shows any evidence of an anatomic lesion. Operation is often useless in these cases. The purpose of this study was to determine, if possible, whether the electroencephalogram could clarify the clinical picture and make operative indications more certain. It was also designed to compare the results of the three methods of clinical investigation—the electroencephalographic, the pneumoencephalographic and the neurologic—to learn whether there is agreement between them and, if so, what such agreement might mean.

MATERIAL AND METHOD

The material consisted of 17 children from 7 months to 11 years and 10 months of age who presented focal convulsive seizures. Of these, 10 had only focal seizures; in 6 an entire half of the body, in 1 only the face and arm, in another the arm and leg and in 2 only the face was involved. The remaining 7 children showed both focal and general convulsions. In 3 of them the focal attacks preceded the generalized convulsions, and in 4 the generalized convulsions became unilateral before they terminated.

Routine electroencephalograms were taken according to the standard procedure involving simultaneous tracings from three electrodynamic ink writers driven by uniform, independent, resistance-capacity–coupled amplifying units. The electrodes were lead cups 7 mm. in diameter which were filled with Sanborn electrocardio-

This work was made possible through the encouragement of and facilities supplied by Dr. Bernard Sachs, when he was Director of the Division of Child Neurology.

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Division of Child Neurology, Neurological Institute of New York.

gram paste and cemented to the scalp with collodion. As a basis for bipolar recording, eighteen to twenty-two electrodes were placed routinely on the scalp over standard positions, supplemented by additional electrodes as required in the delimitation of any observed focal disturbance (fig. 1). In addition reference electrodes were sometimes placed on the lobes of both ears for monopolar recording. During the examination the patient lay at rest on a bed within an electrically shielded chamber under constant observation by a nurse, who reported periodically on the child's condition and also signaled spontaneous body movements, blinking, and the like. When occasion demanded, the experimenter could also observe the child from outside through a window in the recording chamber.

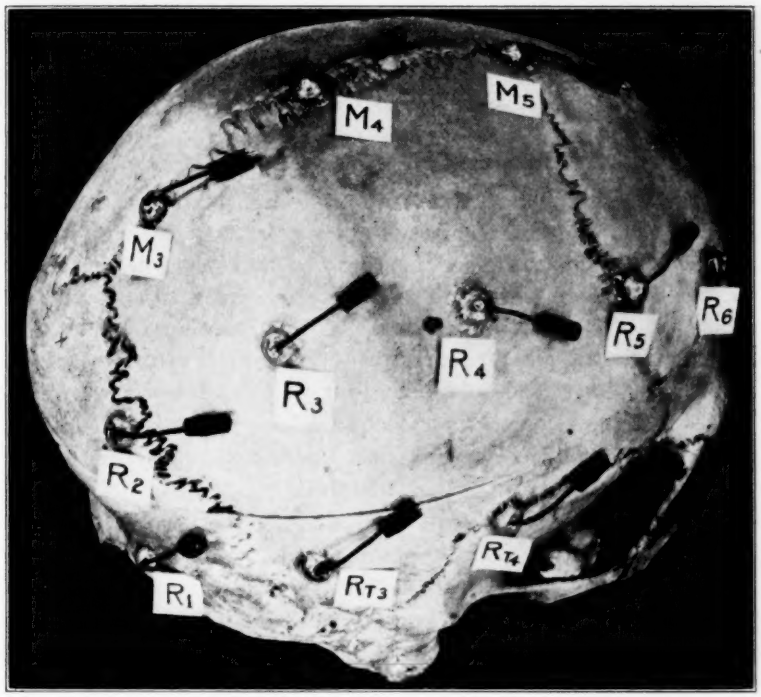

Fig. 1.—Photograph showing standard electrode placements on a skull as viewed from the right. M_4 is at the superior rolandic point and R_4 approximately over the central fissure. (A line through M_4 and R_4 has an anterior included angle with the midline of 70 degrees.) R_{T4} is approximately 5 cm. directly above the auditory meatus. The R line of electrodes is roughly concave medially, with R_1 (at the level of the inion) 3 to 4 cm., R_4 (central) 7 cm., and R_6 (anterior frontal) 5 to 6 cm. to the right of the midline. Interelectrode distances in the M and R lines usually vary between 4 and 5 cm. The R and R_T leads are duplicated by electrodes placed on homologous positions over the left hemisphere.

RESULTS

The electroencephalographic findings revealed a wide variability in the composition of the pathologic pattern in individual cases. At the

same time, certain underlying consistencies were apparent. "Slow" waves were in some degree a universal pathologic feature of the records. Varying in rate from 1 per second to frequencies merging imperceptibly into the normal alpha rhythms, these slow components showed all shades of regularity and dominance. They ranged from continual grossly abnormal, large epileptiform discharges, completely obliterating any semblance of normal alpha activity, through less prominent random sequences or intermittent paroxysmal bursts to scattered low voltage waves superimposed on prevailing normal alpha rhythms. Faster epileptiform discharges (spikes) were prominent in the records of 13 of the patients, appearing either as unattached single or serial discharges (cases 4, 11, 13, 15 and 17) or in combination with some of the slow waves, producing a variety of wave-spike contours [1] (cases 1, 2, 6, 7, 8, 9, 12 and 14). Of the remaining 4 cases, the records in 2 revealed what were interpreted as doubtful epileptiform effects. These included in 1 instance (case 5) an occasional suspicious spiking of the occipital alpha waves on one side and in the other (case 10) a prominent serial fast discharge comparable in frequency to the spikes noted in other cases, but noticeably smaller in amplitude (compare case 13). In the remaining 2 cases (3 and 16) abnormal slow waves with none of the paroxysmal features already noted were exhibited. The electroencephalograms in all 17 cases showed bilateral differences of varying degree. In 11 cases there was a noticeable lateralization of pathologic activity to one side, which in case 3 appeared only under stress of hyperventilation. In 3 additional cases (5, 15 and 16) there was no consistent bilateral difference in the abnormal patterns present but the normal alpha waves showed a noticeable lateralization to one side. In the remaining 3 cases of the series (8, 10 and 11) conflicting bilateral differences in the type and amount of abnormal activity were exhibited. In 9 cases restricted foci of pathologic discharge appeared. In 5 of these (cases 4, 6, 7, 9 and 11) the foci were unilateral; in 3 others (cases 3, 8 and 17) they were bilateral over homologous areas, and in the last (case 16) the focus appeared over the midline. Intermittent scattered foci were present in 5 additional cases (1, 2, 12, 13 and 14), and in the remaining 3 cases (5, 10, 15) no foci were observed.

REPORT OF CASES

Group A 1.—*Patients having focal seizures only with no disturbance of consciousness during the attack.*

1. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electroencephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133-1148 (Dec.) 1935. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, ibid. **39**:314 (Feb.) 1938; Influence of the Blood Sugar Level on the Wave and Spike Formation in Petit Mal Epilepsy, ibid. **41**:1111-1116 (June) 1939.

CASE 1.—A child aged 7 months had had attacks affecting simultaneously the right side of the face, the right arm and the right leg several times a day since the age of 1 month. There were hyperreflexia on the right side and paresis of the right arm; the right optic disk was pale. A ventriculogram showed that the ventricles were not enlarged but were asymmetric, the left being smaller than the right. The electroencephalogram revealed grossly pathologic large, slow waves at 1 to 4 per second, with intermittent associated spikes of lower amplitude at 15 to 20 per second over both sides, but better defined on the right. Recurrent foci for these waves were present over both central areas and extended posteriorly to the occipital region on the right. The normal occipital alpha waves, at 6 per second, were intermittent and poorly defined.

CASE 2.—A child aged 3 years 8 months had had left-sided attacks of variable distribution several times a day for the past one and a half years. The intelligence quotient was 127. There were left hemiparesis with hyperreflexia and strabismus to the left. The pneumoencephalogram showed asymmetric ventricles, the right being larger than the left. Exploration revealed mild chronic inflammation of the cortex (see "Comment"). The electroencephalogram showed large, markedly

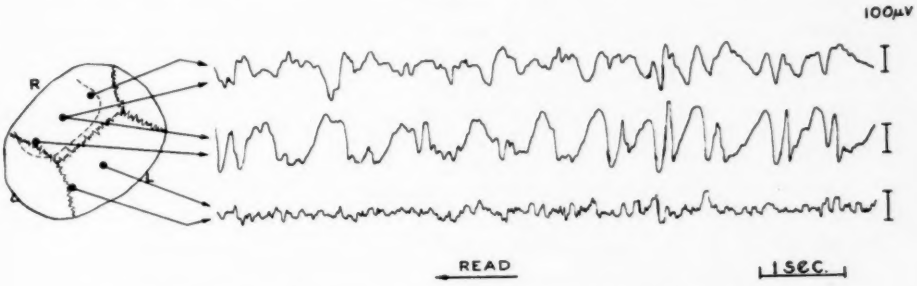

Fig. 2.—Electroencephalogram of a patient (case 2) with left-sided attacks, showing marked lateralization of abnormal slow waves to the right side. In this figure and in figures 3 and 4, the calibrations are 100 microvolts from peak to peak, the length of a one second interval is indicated at the bottom of the figure and tape direction is indicated by the arrow. The dotted line represents the operative flap.

abnormal, slow waves at 1 to 5 per second with recurrent associated spikes of lower amplitude at 8 to 20 per second strongly lateralized to the right side and greater in amplitude over the sensorimotor and frontal regions. Recurrent scattered foci occurred most often in the right central and premotor areas (fig. 2).

CASE 3.—A child aged 4 years 3 months had had attacks occurring simultaneously in the right arm and the right leg, preceded by pains in the right arm, several times a day for one month before admission. The intelligence quotient was 149. Neurologic examination revealed nothing abnormal. The pneumoencephalogram showed asymmetric ventricles, the left being larger than the right, which was considered of normal size. Exploration revealed that the cortex was hyperemic, with distention of the arachnoid (see "Comment"). The electroencephalogram showed abnormal slow activity, including random waves of low amplitude at 2 to 3 per second and rhythmic waves of medium amplitude at 4 to 6 per second over both sides, intermixed with normal alpha rhythms, at 8 to 9 per second. Recurrent foci for the 4 to 6 per second waves were found over both

temporal regions. No consistent bilateral differences were noted in the resting state, but during hyperventilation there was marked accentuation of the 4 to 6 per second activity, more pronounced on the right.

CASE 4.—A child aged 5 years 3 months had had convulsive movements of the left side of the face three to four times a day for four months before admission. The intelligence quotient was 121. Neurologic examination showed some weakness of the left side of the face. A pneumoencephalogram revealed that the vault of the skull was thin, with a large venous plexus in the left frontal region; the ventricles were somewhat enlarged symmetrically. The electroencephalogram showed intermittent foci of 15 to 20 per second single spikes of medium to large amplitude over the right sensorimotor region, with a restricted focus over the inferior central-temporal region, and random slow waves at 2 to 6 per second over both sides, the slower (2 to 3 per second) components being larger posteriorly and the 4 to 6 per second waves being better defined over the region of the spike focus on the right side than over the homologous area on the left. Normal alpha activity was somewhat more distinct on the right.

CASE 5.—A child aged 9 years 11 months had convulsions starting with twitchings of the left side of the face and then involving simultaneously the left side of the face, the left arm and the left leg. These had occurred about once a month for the past year. The intelligence quotient was 99. Neurologic examination disclosed only varying left homonymous hemianopia with some nystagmus to the left. A roentgenogram showed that the vault of the skull was thin, with vascular anomalies in the right parietal region. On account of the latter, pneumoencephalographic examination was not made. The electroencephalogram showed scattered slow, 3 to 6 per second waves of low amplitude over both sides, the amplitude being greater over the occipital and parietal lobes. There were normal occipital and central alpha rhythms, which were less well defined on the right side. Occasional doubtful "spiking" of alpha waves appeared on the left.

CASE 6.—A child aged 7 years 2 months had had convulsive attacks limited to the right side of the face two to three times a month for the previous year. Unconsciousness was probably not present during the attacks. The intelligence quotient was 91. Neurologic examination revealed awkwardness of the right arm, nystagmus to the right and a tendency of the right eye to drift inward. A pneumoencephalogram showed asymmetric ventricles, the left being larger than the right. The electroencephalogram revealed slow, 3 to 5 per second waves of large amplitude and associated 15 to 20 per second spikes over the left side, with a sharp focus over the left inferior central-temporal region. Low amplitude waves at 3 to 5 per second without the spike component appeared on the right side.

Group A 2.—*Patients having focal seizures only with unconsciousness during the attacks.*

CASE 7.—A child aged 4 years 5 months had had attacks involving simultaneously the right side of the face, the right arm and the right leg once a week since the age of 1 month. The intelligence quotient was 110. Neurologic examination revealed weakness of the right side of the face. A pneumoencephalogram showed an old depressed fracture in the left parietal region, but the ventricles were equal and of normal size. Exploration showed abnormal-looking cortex under the fracture and excessive subarachnoid fluid. The fracture was elevated, but the cortex was not excised (see "Comment"). The electroencephalogram revealed a sharply defined focus of waves and spikes of large amplitude over the lateral

aspect of the left frontal lobe 6 cm. anterior to the site of the old depressed fracture. The spikes, at 12 to 25 per second, were restricted to the left frontal region, but the slow waves, at 3 to 5 per second, appeared generally over both sides, but more frequently on the left with secondary foci over the occipital lobe, which corresponded apparently to the area of origin of the occipital alpha waves (fig. 3).

CASE 8.—A child aged 7 years 8 months had attacks involving simultaneously the right side of the face, the right arm and the right leg, with the greatest movements in the arm. These had been present for four and a half years and occurred in series several times each night. The intelligence quotient was 104. Neurologic examination revealed hyperreflexia with transitory paresis of the right side following convulsions. The pneumoencephalogram was negative. The electroencephalogram showed pathologic slow waves at 2 to 6 per second diffusely scattered over both sides and interspersed with waves of large amplitude at 3 per

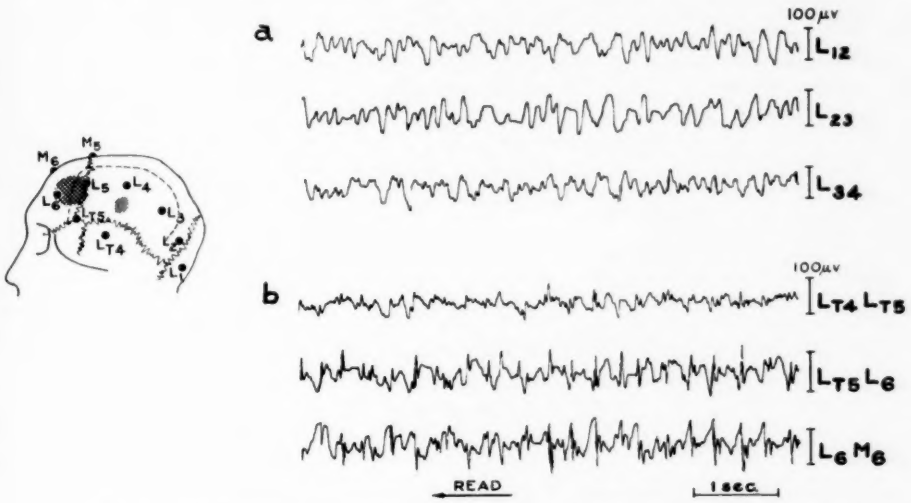

Fig. 3.—Electroencephalogram showing pathologic foci encountered in a patient (case 7) with right-sided focal attacks. In both *a* and *b* the lead designations are given at the right and refer to the corresponding electrode positions shown in the drawing at the left.

In *a*, note the recurrent "secondary" foci of 4 to 6 per second waves occurring over the anterior occipital (L_2) and parieto-occipital (L_1-L_3) areas. The approximate position of the atrophic area demonstrated at operation is indicated by the small shaded area just lateral to L_4. Note the absence of wave-spike discharge in this area (i. e., in lead L_{34}). The dotted line indicates the position of the operative flap.

In *b* is shown the primary wave-spike focus as recorded more anteriorly over the left frontal lobe. The cross-hatched area indicates the area of this focus with the focus shown at L_6.

second and spikes at 10 to 20 per second. The waves and spikes showed recurrent foci over both postcentral areas, with more spikes on the right. Over the frontal lobe the 5 to 6 per second waves were noticeably lateralized to the left.

CASE 9.—A child aged 8 years had had attacks involving simultaneously the left side of the face and the left arm once or twice a week for three and a half years. Neurologic examination gave normal results except for questionable blurring of both optic disks. The pneumoencephalogram showed some flattening of the right frontal horn. The electroencephalogram revealed a consistent focus of slow, 3 per second waves of large amplitude and associated spikes at 15 per second over the left inferior central area. Although the spike components were sharply lateralized to the left side, the slow waves were present on both sides and were best defined on the right side over the inferior central-temporal region—an area approximately homologous to the left central focus already mentioned. Occasional foci of slow, 3 to 5 per second waves were found over the occipital lobes.

CASE 10.—A child aged 9 years 9 months had attacks involving simultaneously the right side of the face and the right arm or the entire right side, with prodromal paresthesias in the right ear in some of the attacks. The patient was sometimes conscious during the seizures. The attacks had occurred every two to three months for one year. The intelligence quotient was 110. Neurologic examination showed hyperreflexia on the right side. The pneumoencephalogram revealed nothing abnormal. The electroencephalogram showed slow, 3 to 6 per second waves of low to medium amplitude and prominent irregular, serial fast discharges at 15 to 25 per second over both sides, especially in the sensorimotor area. The slow components were questionably greater on the left, while the fast waves were noticeably better defined on the right; dominant normal occipital alpha rhythm, at 11 per second, was present.

Group B 1.—*Patients with focal and general seizures, the focal attacks preceding the general.*

CASE 11.—A child aged 11 years 1 month had had attacks starting in the right arm and extending to the right leg before becoming general two to three times a week for the past three years. The intelligence quotient was 65. Neurologic examination revealed poor coordination in the right arm and a questionable Babinski sign on the right. The pneumoencephalogram showed that the right temporal horn did not fill with gas. It was considered by the roentgenologist to be normal. The electroencephalogram revealed medium to large, slow waves at 2 to 6 per second appearing diffusely over both sides, being better defined on the right, and showing intermittent scattered foci. Intermittent single spikes at 15 to 20 per second of medium amplitude were restricted to the left side, with a sharp focus over the left central area.

CASE 12.—A child aged 6 years had had attacks beginning in the left side of the face and left hand and spreading to the left arm and leg about once a month for the past four and a half years. For one year petit mal attacks had followed these seizures. The intelligence quotient was 99. Neurologic and pneumoencephalographic examinations were negative. The electroencephalogram showed large, slow waves at 2 to 6 per second with occasional associated spikes at 15 to 20 per second occurring generally over both sides, but especially on the right. Slow waves, larger over the parietal and occipital regions, and spikes, more noticeable over the sensorimotor areas, were observed. Intermittent scattered foci were seen.

CASE 13.—A child aged 7 years 5 months had attacks starting with dysesthesias about the mouth and twitching of the right side of the face and head and progressing to generalized convulsion with unconsciousness. Three of these attacks had occurred one and a half months before admission and none since.

The intelligence quotient was 103. Neurologic examination revealed weakness of the right side of the face. The pneumoencephalogram showed absence of gas in the right ventricle, but otherwise nothing abnormal. The electroencephalogram revealed medium to large, slow waves at 2 to 5 per second and irregular smaller, fast waves at 20 to 25 per second occurring generally over both sides, without consistent bilateral difference. Intermittent single spikes at 15 per second were present over the parietal and occipital lobes on both sides, mostly on the left. The single spikes and the faster serial waves showed variable scattered foci. Recurrent phase reversals for slow waves occurred over both parieto-occipital areas.

Group B 2.—*Patients with general convulsions that became focal before they terminated.*

CASE 14.—A child aged 6 years 2 months had had generalized convulsions of four hours' duration, becoming right sided with variable distribution as conscious-

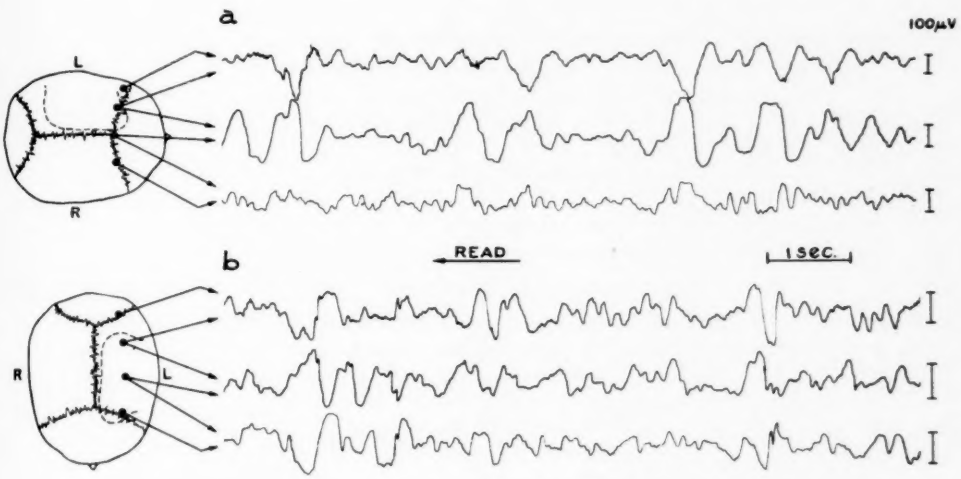

Fig. 4.—Electroencephalograms of a patient (case 14) having both generalized and right-sided attacks.

(*a*) Gross lateralization of large pathologic, slow discharge to the left side with recurrent foci over the left motor region.

(*b*) Pathologic patterns encountered with anteroposterior leads placed over the left side. Note recurrent foci over the sensorimotor region.

The dotted line indicates the position of the operative flap.

ness returned, several times a day for the past fourteen months. The intelligence quotient was 81. Neurologic examination revealed right hyperreflexia with transient right hemiparesis. The pneumoencephalogram showed that the vault of the skull was thin. The ventricles were asymmetric, the left being larger than the right. Exploration revealed arachnoid adhesions (see "Comment"). The electroencephalogram showed grossly pathologic large, slow waves at 1 to 5 per second with intermittent associated spikes at 8 to 20 per second diffusely scattered over both sides, particularly on the left. The amplitude was greater over the central and frontal regions than posteriorly, with scattered foci in the central regions (fig. 4).

CASE 15.—A child aged 8 years 5 months had attacks of generalized nocturnal convulsions, with movements involving only the right side of the face and the right arm as consciousness returned. Three such attacks occurred in the two months before admission. The intelligence quotient was 112. Neurologic examination gave normal results. The pneumoencephalogram showed that the coronal sutures were rather wide. No gas was present in the right ventricle; the left ventricle was enlarged. There was no displacement. The electroencephalogram showed abnormal slow, 3 to 6 per second waves of medium amplitude and recurrent spike discharges at 15 to 20 per second over both sides, with the spike discharges mostly in the sensorimotor and frontal areas. The pathologic activity showed no consistent bilateral difference, but the normal occipital alpha rhythm, at 8 to 9 per second, tended to be less well defined on the left.

CASE 16.—A child aged 9 years 9 months had had generalized convulsions terminating in convulsive movements which spread from the left arm to the left side of the face and the left leg, without unconsciousness, several times a day for the past year. The intelligence quotient was 97. The neurologic examination was negative. The pneumoencephalogram revealed that the vault of the skull was thin and that the left ventricle was larger than the right, the latter being considered of normal size. The electroencephalogram showed pathologic irregular, slow, 2 to 6 per second waves of low to medium amplitude, which were generalized over both sides, with no consistent bilateral difference; an intermittent focus of 4 per second waves over the midline in the premotor area; normal occipital alpha waves, less well defined on the right, and, during overbreathing, greater and more prolonged accentuation of the slow components on the right.

CASE 17.—A child aged 11 years 10 months had had generalized nocturnal convulsions, terminating in movements which spread from the left side of the face to the left arm and leg with returning consciousness, once a week for the past three years. The intelligence quotient was 93. No abnormal neurologic signs were noted. The pneumoencephalogram was normal. The electroencephalogram revealed over both sides irregular, slow waves at 2 to 6 per second intermixed with normal alpha waves, at 9 to 10 per second, and intermittent 10 to 15 per second spikes of large amplitude. The spikes were larger and more frequent over the sensorimotor areas and were occasionally combined with a slow, smooth, 3 per second wave, more noticeable on the right. A consistent focus for these waves occurred over the right inferior central region. Less frequent and less consistent phase reversals were present over the homologous area on the left.

COMMENT

The purpose of this investigation was to determine the value of electroencephalographic evidence in focal convulsive seizures. It should be noted at the start that in none of our cases were the pathologic changes restricted to any one part or to either side of the brain. In our experience focal cortical convulsions differ from general convulsions electroencephalographically only in that one part of the brain is more apt than the rest to exhibit pathologic wave alterations. While there tended to be a rough sort of relationship between the part of the brain with the greater wave alterations and the location of the convulsions, this was

not a uniform finding. Fourteen of our patients showed some bilateral differences in the electroencephalograms, 11 having a unilateral predominance of pathologic activity and the other 3 differences in definition of the normal alpha rhythms on the two sides. Of these 14 patients, 11 had attacks on the contralateral side and 3 on the ipsilateral side, and the remaining 3 patients exhibited a variable relationship. In 8 patients (cases 2, 4, 6, 7, 12, 13, 14 and 17) the seizures were on the side opposite that of the predominant abnormal discharges, and in the other 3 (cases 5, 15 and 16) they were contralateral to the side of the more poorly defined normal alpha rhythms. Three patients (cases 1, 3 and 9) had attacks ipsilateral to the greater pathologic activity. In the case of the remaining 3 patients the relationship between the electroencephalographic findings and the attacks was extremely variable. Thus, the patient in case 8, showing bilateral waves and spikes, with the spikes more pronounced on the right, had seizures on the right side. There was, however, a noticeable lateralization of the 5 to 6 per second waves to the left frontal lobe. In case 10 the attacks occurred on the right side, contralateral to the slow waves and ipsilateral to the irregular serial fast discharges. In case 11, on the other hand, the attacks were on the right side, contralateral to the spikes and ipsilateral to the slow waves.

Another interesting finding was that the gross contralaterality of pathologic change in the electroencephalogram was observed less consistently in the patients of group A, in whom the attacks were only focal, than in those of group B, in whom the focal attacks were part of the general attacks. Thus, all of the patients in group B showed pathologic wave patterns contralateral to the attacks, while only 5 in group A showed such contralaterality.

In contrast to this was the occurrence of sharply localized foci of abnormal activity, which were observed much more frequently in patients having only focal attacks. In all, 9 patients showed restricted foci of pathologic discharge, and 7 of these were in group A. In 4 patients (cases 4, 6, 7 and 11) the convulsions were contralateral to the foci and in 1 (case 9) ipsilateral. The remaining 2 patients had bilateral homologous foci. Of 2 patients in group B, 1 (case 16) showed intermittent phase reversals over the midline in the premotor region and the other (case 17) wave and spike foci over both central areas, but more frequent and consistent on the side opposite the focal attacks.

Especial interest attaches to the type of restricted unilateral foci of spikes or wave and spikes noted in 5 of our patients (cases 4, 6, 7, 9 and 11) from the standpoint of their possible reliability as an indicator of underlying gross operable lesions. That such foci may signalize underlying organic cortical damage is indicated by the recent observations

of Case and Bucy,[2] who, in a series of 11 cases, found epileptiform spikes overlying cortical lesions in 3 and wave and spikes in 1. The lesion involved was a meningioma in 2 cases and an osteoma in 1 case. In the fourth case, in which no operation was performed, there was evidence of local damage to the brain in association with a bony defect. The only direct evidence on this point in the present series arises from the 1 case of the group under consideration (case 7) in which operation was performed. In this case, as has been noted, operation revealed a small atrophic area at an appreciable distance from the region of the preoperative wave and spike focus (fig. 3). The latter in this instance presumably reflected an area of physiologic disturbance in the cortex which may have been functionally related to the demonstrated lesion. Of the remaining 4 cases in which similar foci were shown, case 9 was the only one in which the electroencephalographic evidence did not appear to be in line with the clinical findings. One might question the presence in this case of a gross operable lesion corresponding to the wave and spike focus observed in the left central region, since all other evidence pointed to the right hemisphere as the seat of involvement.

It appears that restricted consistent foci of epileptiform discharge in certain cases may be indicative of underlying organic cortical damage. Pointing out this fact, Gibbs [3] has suggested the advisability of surgical exploration when such a focus is encountered, in the hope that a gross operable lesion may be found. Whether or not such a procedure is justified will depend ultimately on the empiric determination of the predictive reliability of such foci.

Bilaterally symmetric foci of the type observed in 3 patients (cases 3, 8 and 17) presumably reflect a dynamic functional interplay between homologous cortical areas. It is not impossible that bilaterally homologous cortical areas exercise an influence on each other. Hence pathologic activity in any focus may cause not only contralateral seizures but, by this action on the contralateral homologous area, ipsilateral attacks as well.

Of the two newer technical methods of investigating the nervous system as an aid to diagnosis—the pneumoencephalographic and the electroencephalographic—each has a field of its own, in the main independent of the other. Each method reveals totally different things. The pneumoencephalogram shows gross alterations of anatomic structure; the electroencephalogram reveals alterations of cortical physiologic activity, which may possibly have no histopathologic basis. As was to be expected in this series of cases, the pneumoencephalogram

2. Case, J. T., and Bucy, P. C.: Localization of Cerebral Lesions by Electroencephalography, J. Neurophysiol. **1**:245-261, 1938.

3. Gibbs, F. A.: Electroencephalography in Epilepsy, J. Pediat. **15**:749-762, 1939.

offered far less striking evidence than did the electroencephalogram. The latter showed pathologic alterations of one sort or another in all of our 17 cases, while the former revealed nothing of significance in 6 of the 16 cases in which it was employed. In case 1 the ventricles were eventually visualized by means of ventriculograms. Of the 10 cases in which pneumoencephalographic findings were positive, asymmetric ventricles were shown in 6 (1, 2, 3, 6, 14 and 16) and symmetrically enlarged ventricles in 2 (4 and 12). In 1 case no gas entered one of the ventricles, and in the last (case 9) flattening of the anterior horn on the side opposite that of the convulsions was noted.

Of the 6 cases in which asymmetric ventricles were shown, the larger ventricle was on the side opposite that of the convulsions in 4 and on the same side in 2. Electroencephalographic studies in the same 6 cases gave results that seemed to prove that the two methods test different things. Thus, in 3 cases (2, 6 and 14) the greater pathologic activity shown in the electroencephalogram was on the side of the larger ventricle and the attacks were on the opposite side. In case 1 the attacks were contralateral to the side of the smaller ventricle, while the greater changes in the brain waves were on the side of the larger ventricle, ipsilateral to the attacks. In case 3 the larger ventricle was contralateral to the attacks while the greater electroencephalographic changes were ipsilateral, and in the remaining case (16) this relation was reversed. In case 9, in which there were flattening of the right frontal horn and left-sided attacks, the greater pathologic activity of the brain was observed on the left side.

In 4 of our cases surgical exploration was carried out, the results of which will be reported here at greater length. In case 2 there were left-sided attacks, hyperreflexia and paresis involving the left side and asymmetric ventricles, with greater enlargement of the right. A right frontoparietal osteoplastic flap was elevated. The subarachnoid fluid seemed moderately increased; the gyri in the operative field were somewhat atrophic and firm to the touch, and the sulci were widened. The motor gyrus was more vascularized than the surrounding cortical gyri, suggesting that it may have been the seat of inflammatory disease. There were no adhesions, and the dura and the arachnoid both appeared normal. On stimulation of the motor gyrus, the only movement observed was a flickering of the fingers of the left hand. No radical surgical treatment was attempted. The preoperative electroencephalographic findings (fig. 2) in this case, with strong lateralization to the right side and evidence of maximum disturbance over the sensory motor and frontal regions, would appear to be in harmony with the rather diffuse cortical changes observed at operation.

A left temporoparietal craniotomy was performed in case 3, in which there was a history of right-sided attacks for one month before

operation. The roentgenogram of the skull and the neurologic findings were normal, but the left (contralateral) ventricle was enlarged. The dura was found to be tense, and the underlying cortex was hyperemic. The gyri were slightly narrowed and the sulci widened, and there were lakes of cerebrospinal fluid between the gyri. Abnormal arachnoid granulations were noted over the precentral and postcentral gyri. The dura was approximately 0.8 mm. in thickness. Two large veins entered the granulations, one draining the postcentral and the other the precentral gyrus. Preoperative electroencephalograms in this case had indicated diffuse bilateral changes with recurrent foci of 4 to 6 per second waves over both temporal lobes and evidence of lateralization to the right, which was present under hyperventilation only.

In case 7 roentgenograms showed a small area of flattening in the inferior portion of the left parietal bone, suggestive of an old depressed fracture. The electroencephalogram gave evidence of an area of maximum cortical disturbance approximately 6 cm. anteriorly, over the frontal lobe, in the form of a focus of large wave and spike discharge. While the spikes (at 12 to 25 per second) were restricted to the left frontal lobe, the slower wave component (at 3 to 5 per second) appeared generally over both sides, was lateralized to the left and showed additional recurrent foci more posteriorly, over the anterior portions of both occipital lobes (fig. 3). This case is of special interest because of the focal but somewhat divergent nature of the preoperative roentgenographic and electroencephalographic findings. The operative diagnosis in this case was that of a cortical scar and atrophy of gyri in the left frontoparietal region. The atrophic area was about ¾ inch (1.9 cm.) in diameter and was situated just above the sylvian point and underlying the point of fracture noted in the roentgenogram. This area was slightly indented, firmer to touch than the surrounding brain and whiter. There was also some increase in subarachnoid fluid overlying the depression, and one blood vessel formed a tight "S" over the area. The inner table of bone at the point of fracture, as seen roentgenographically, was smooth and unbroken. There was no indication of depression into the brain cavity and no evidence of pathologic pressure on the underlying cortex. The dura was intact and normal, and there were no adhesions either between dura and bone or between dura and cortex. Electrical stimulation of the cortex yielded no response whatever. Because of its location and the doubtful causative relation between the small amount of observed surface change and the clinical symptoms, no attempt was made to excise the atrophic area. In this connection the lack of correspondence between the point of maximum cortical physiologic disturbance as indicated by the electroencephalogram and the location of the observed anatomic lesion should be noted. If the anatomic lesion in question is

regarded as the source of pathologic irritation underlying the child's attacks, then it would appear necessary to recognize the possibility that local damage to the brain of this nature may, in certain instances, be associated with maximum cortical electrical disturbance at an appreciable distance from the lesion. A second electroencephalogram made ten days after exploration revealed the preoperative focus to be still present and apparently unchanged.

A left frontoparietal craniotomy was carried out in case 14, in which there were right-sided attacks, transient paresis and hyperreflexia involving the right side, a normal roentgenogram of the skull except for an unusually thin vault and asymmetric ventricles with greater dilatation on the contralateral (left) side. There was slightly more fluid than usual in the subarachnoid space, but the cortex appeared normal. Electrical stimulation of the precentral and postcentral gyri close to the midline initiated focal movements similar to those observed during the child's attacks. Preoperative electroencephalographic study in this case had revealed grossly pathologic diffuse, slow patterns, with a strong lateralization to the side of the larger ventricle (left) and evidence of maximum involvement over the central and frontal regions. A second electroencephalogram made one month after operation showed this picture to be grossly unchanged (fig. 4).

CONCLUSIONS

A series of cases of so-called focal cortical seizures has been studied by electroencephalographic, pneumoencephalographic and clinical neurologic methods.

In none of these cases did electroencephalographic studies show that purely focal cortical disturbances were responsible for the seizures. The abnormal rhythms were diffuse in all cases, but there was a definite tendency for these waves to be more prominent on the side opposite that of the convulsions. No one type of pathologic waves was found exclusively. Focal cortical seizures and generalized convulsions differ from each other only in the fact that in the former electroencephalographic abnormality tends to be present more on one side of the brain than on the other, and sometimes to be even more closely localized.

The clinical neurologic and the electroencephalographic findings bore closer relationship to each other and to the laterality of the convulsions than did the pneumoencephalographic changes, which gave little contributory data in most cases.

Only those cases in which the results of all three methods of investigation agree as to the location of a focal lesion are suitable for surgical exploration.

Technical and Occasional Notes

CHANGES IN RETINAL ARTERIES BEFORE CONVULSIONS INDUCED BY ELECTRIC SHOCK

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The role of the vascular bed has long been of interest to epileptologists.[1] Kennedy [2] mentioned the whitening of the brain at operation preceding a convulsion, and Foerster [3] noted preparoxysmal anemia of the brain so frequently that on the basis of its occurrence he could predict the subsequent onset of the convulsion. However, Penfield, von Santha and Cipriani [4] stated that "vascular spasms and anaemias may be concerned in the background of epilepsy but at all events they play no role in the actual mechanism during a seizure." After measuring the blood flow in the jugular veins thermoelectrically, Gibbs, Lennox and Gibbs [5] concluded that their evidence was against the theory of widespread anemia of the brain as an immediate cause of epileptic seizures.

The work just mentioned, especially the observations at the operating table, in the main has been done on patients who, for various reasons, were subject to spontaneous epileptic attacks. The state of the retinal arteries may be considered the simplest observable index of the state of the cerebral vessels. During the course of the electric shock treatment of psychoses at the New York State Psychiatric Institute and Hospital, opportunities were given to examine the retinal arteries before and after the electric shocks were administered. None of the patients were suffering from convulsive disorders. From all subjects epileptoid convulsions of the type described were obtained if a sufficiently high voltage was used. These convulsions in general were apparently similar in pattern of discharge to the usual attacks occurring spontaneously in

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2. Kennedy, F.: Epilepsy and the Convulsive State, Arch. Neurol. & Psychiat. **9**:567 (May) 1923.

3. Foerster, H. O.: Die Pathogenese des epileptischen Krampfanfalles, Deutsche Ztschr. f. Nervenh. **94**:15-53, 1926.

4. Penfield, W.; von Santha, K., and Cipriani, A.: Cerebral Blood Flow During Induced Seizures in Animals and Man, J. Neurophysiol. **2**:257-267 (July) 1939.

5. Gibbs, F. A.; Lennox, W. C., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, Arch. Neurol. & Psychiat. **32**:257-272 (Aug.) 1934.

man. The method devised by Bini [6] was employed in accordance with the technic described by Kalinowsky and Barrera.[7] The treatments were carried out by Drs. Barrera, Kalinowsky and Horwitz. It is found that most electrically induced generalized convulsions are preceded by a period of unconsciousness varying from a few to even fifty or sixty seconds. In many cases this period cannot be distinguished from states of unconsciousness, similarly induced, which are not followed by generalized convulsions. It was during such states of "absence" that I attempted to observe changes occurring in the retinal arteries.

TECHNIC

Just before the electric shock was given an artery near the disk was observed with an ordinary May ophthalmoscope and an attempt was made to fix the width and appearance of this vessel in the mind's eye. After the shock an attempt was made to return as quickly as possible to observation of the previously noted artery. Although the time given is an approximation, only rarely could the vessel be fixated again in less than six or seven seconds. In many cases it could not be observed again at all for various reasons, of which the most prominent are mentioned here: The patient sometimes had a convulsion immediately and the eye promptly rolled out of the field of vision. Subjective difficulties interfered with viewing the vessel. It was regularly impossible to observe the vessel continuously from before the passage of the current through the subsequent period of "absence," since at the moment of passage of the current the patient immediately jerked violently and blinked spasmodically. Despite technical difficulties, 25 observations were made over a period of several months, 14 of which were considered good and fair. The terms "good" and "fair" refer to my subjective feeling of certainty that the observation was accurate. All other observations were disregarded.

OBSERVATIONS

The results of the 14 observations which were recorded as "good" are summarized as follows: In 7 cases a vessel observed previous to the passage of the electric shock showed a definite constriction during the period of "absence" before the convulsion itself started. The time during which this constriction was noted varied from about five to ten seconds before the onset of the attack. Conversely, in 6 cases the vessel observed during the period of deep "absence," starting from seven to ten seconds after the passage of the electric current, neither constricted nor became narrower than when seen before the application of the shock. In none of these 6 cases did a convulsion follow the "absence." In 1 case a vessel observed steadily from approximately seven to fifteen seconds after the shock remained normal in size; observation was then discontinued, and thirty seconds later the patient had a convulsion. In 1 observation recorded as "good," but which was unusual in that the vessel was seen in about three to four seconds after the passage of current, the vessel dilated and then constricted to its normal size in about the next two seconds after passage of the current, where it remained during the entire period of "absence." This observation is also recorded among the 5 cases in which a convulsion did not take place and narrowing did not occur.

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6. Bini, L.: Electroshock-Behandlung, in Troisième Congrès neurologique international, comptes rendus, Copenhagen, Ejnar Munksgaard, 1939, p. 706.

7. Kalinowsky, L., and Barrera, S. E.: Electric Convulsion Therapy in Mental Disorders, Psychiatric Quart. **14**:718-730 (Oct.) 1940.

Of the 11 observations which were considered "fair," 3 showed constriction of the artery before a convulsion and 4 revealed that no constriction occurred during the period of "absence" which was not followed by a convulsion. However, in 3 of the cases in which no convulsion occurred the impression of mild constriction was obtained at some time during the period of "absence," and in the fourth case the artery, which was seen within three or four seconds after the passage of the current, gave an impression of being wider than it formerly had been. It seemed to return to its former size within one or two seconds and remained so.

SUMMARY AND CONCLUSIONS

These observations may be summarized as follows:

The electric shock per se has no prolonged effect on the artery, and any immediate effect is one of dilatation, as indicated by the 2 observations made in three to four seconds after the passage of the current.

In all cases in which a sufficiently prolonged period of unconsciousness precedes the active convulsive state the retinal arteries constrict prior to the onset of the convulsion.

In the majority of cases in which no retinal constriction occurs during the period of "absence" no convulsion occurs. Three observations out of 13 tended to refute this as a general rule.

From the preceding observations, one may conclude that in cases of convulsions following electric shock a spasm of the retinal arteries, during the "absence," usually precedes the generalized convulsion and that as a rule a spasm does not occur if the effect of the shock is to give only a "petit mal" seizure or an "absent" state. In addition, if one can infer that the appearance of the retinal artery accurately reflects the condition of the smaller cerebral arteries, one may conclude that the arterial spasm does not cause the convulsion but is itself an early part of the process sent into action by something else, in this case the electric shock.

Obituaries

LASALLE ARCHAMBAULT, M.D.
1879–1940

With the passing of Dr. Archambault the medical profession has lost one of its able neurologists. He was born in Cohoes, N. Y., the son of Dr. Joseph L. Archambault, a physician of that city. As a boy he attended the La Salle School in Troy, N. Y., from which he was graduated with honor. He further distinguished himself in the pursuit of medical studies, graduating from the Albany Medical College in 1902 with prizes for special achievement. Soon after graduation he went to Europe for several years of special training and studied at Berlin, Graz and Paris. There he fell under the influence particularly of Oppenheim and Pierre Marie. To the latter he became endeared, and they corresponded regularly until Dr. Marie's death.

On his return to the United States he decided to pursue his life work in his home community and soon thereafter became associated with the late Drs. Henry Hun and Herman C. Gordinier. In 1906 he was made instructor in neurology in the Albany Medical College; subsequently he held the title of lecturer and adjunct professor, before his appointment as professor of neurology in 1914. This position he filled until 1929, when he was made consultant to the department of neurology. During his years of teaching in the Medical College he was neurologist-in-chief to the Albany Hospital, at the same time caring for a large private practice. From these posts he retired in 1937.

In his earlier years he became greatly interested in dramatics and had considered becoming an actor. His medical teaching bore the imprint of this aptitude. His lectures were rendered fascinating by his ability to dramatize clinical neurologic syndromes. His active interest in neuropathology enabled him to pioneer in this country in bringing to medical students the correlations between necropsy findings and clinical disabilities. He did his own pathologic work, even to the technical details. As a prolific investigator and publisher of numerous scientific studies he inspired all who came in contact with him. He wrote several monographs on the anatomy of the nervous system and contributed to medical literature on poliomyelitis, aphasia, cerebellar atrophy and many other subjects.

Dr. Archambault participated liberally in the programs of local, state and national medical societies. He was a member of the Société de Neurologie de Paris. For thirty years he had been an active member of the American Neurological Association.

In 1918 he was married; Mrs. Archambault survives him. He derived great pleasure from out-of-door sports, music and literature; numismatics was a special hobby.

He championed worthy causes critically and vigorously. He felt it a deep obligation to his patients to keep informed about the advances of science the world over. He did extensive reading of technical studies in three languages. Nevertheless, he often expressed humility about lack of knowledge in his own special field. His influence on his students is reflected in the enviable records made by them in competitive examinations pertaining to the nervous system. He was revered for his charm and his intellectual honesty.

Despite his frail appearance he was an untiring worker, although in his later years he found it necessary to protect his failing health. His devoted wife provided every comfort, in the true French tradition, that his busy professional life and his declining strength required. The end came rather suddenly with bronchopneumonia, on Sept. 28, 1940, in the Albany Hospital, which he had served so many years.

Abstracts from Current Literature

Physiology and Biochemistry

TEMPERATURE AND BRAIN METABOLISM. H. E. HIMWICH, K. M. BOWMAN, J. F. FAZEKAS and W. GOLDFARB, Am. J. M. Sc. **200**:347 (Sept.) 1940.

Himwich, Bowman, Fazekas and Goldfarb report on the effects of changes in temperature on cerebral metabolism. The effect of fever therapy on the cerebral metabolism was studied in 15 patients suffering with dementia paralytica. Observations were made before the rise of temperature and at various intervals while the temperature was elevated. In 7 instances, fever was induced by the injection of 0.4 cc. of vaccine intravenously. In 7 others, the temperature was raised with the inductotherm; in 1 case the patient was studied during malarial fever. The effects were the same with all three methods of induction of fever: the metabolic arteriovenous differences in oxygen content were increased. In 11 of 15 patients the oxygen differences increased at least 2 volumes per cent during fever. The arteriovenous difference in dextrose disclosed absorption of dextrose by the brain in 45 of 49 experiments performed on excised cerebral tissues. No relationship between the volume of oxygen and the amount of dextrose absorbed by the brain was observed. The present results reveal that the brain takes part in the increased oxygen uptake of the body characteristic of fever. In most cases, the augmentation of the arteriovenous difference was greater than could be explained by the rise of temperature. In minced cerebral tissue from rats the increase of respiration at temperatures of 30 to 37 C. is 90 per cent, in accordance with expectation of chemical reactions. In contrast, the rise at temperatures from 37 to 44 C. is only 66 per cent.

MICHAELS, Boston.

VITAMIN C IN EPILEPSY: DILANTIN SODIUM NOT A CAUSE OF VITAMIN C DEFICIENCY. H. H. MERRITT and A. FOSTER, Am. J. M. Sc. **200**:541 (Oct.) 1940.

The occurrence of prominent swelling of the gums in about 3 per cent of their patients under treatment with dilantin sodium led Merritt and Foster to make a study of the vitamin C content of the plasma of 257 ambulatory patients with convulsive seizures. The ranges of the plasma levels of vitamin C and the average values for the three groups of patients receiving (1) no treatment, (2) phenobarbital and (3) dilantin sodium were almost identical. Forty of the 182 patients (22 per cent) who were receiving dilantin sodium therapy had some degree of gingival hyperplasia, which was not present before treatment was begun. The vitamin C content of the plasma bore no relation to the presence or absence of this symptom. The authors conclude that the low level of ascorbic acid in 257 ambulatory patients with convulsive seizures varied beween 0 and 1.6 mg. per hundred cubic centimeters, with an average of 0.45 mg. The ascorbic acid content of the plasma of these patients was in no way influenced by the type of therapy. The long-continued administration of dilantin sodium had no effect on the vitamin C level of the plasma and did not influence the absorption of vitamin C when given by mouth. Hypertrophic gingivitis developing in patients under treatment with dilantin sodium is not related to the vitamin C content of the plasma or of the utilization of the vitamin. The low level of vitamin C in the plasma of clinic patients with epilepsy is due to an inadequate intake of this element, for the administration of food with a vitamin C content to a group with low values resulted in a fivefold increase in the vitamin.

MICHAELS, Boston.

THE CENTRAL NERVOUS SYSTEM STIMULANT EFFECTS OF DEXTRO-AMPHETAMINE SULPHATE. M. PRINZMETAL and G. A. ALLES, Am. J. M. Sc. **200**:665 (Nov.) 1940.

Alles previously found that the comparative physiologic actions of the optically isomeric amphetamines on the mechanisms of the peripheral nervous system were closely similar and that the dextroisomer was more active than the racemic compound or the levoisomer. All compounds were used in the form of their sulfate salts and were administered in aqueous solutions of various concentrations so that the doses were constant in volume and appearance. In 6 cases of narcolepsy, Prinzmetal and Alles report that dextroamphetamine was found to be more effective than racemic amphetamine. Dextroamphetamine was found to be of therapeutic benefit in 4 cases, and a comparison of the relative effectiveness in 2 of the patients showed it to be more effective than similar doses of racemic amphetamine or of levoamphetamine. In 1 carefully studied patient with postural hypotension the dextrocompound proved to be twice as effective as the racemic compound and four times as effective as the levocompound in alleviating the symptoms. Of 13 normal persons, 12 reported that the dextrocompound had a definitely greater stimulating effect than the racemic compound. The pressor effects of the dextroisomer, the racemic form and the levoisomer are closely alike in normal persons. Thus the dextroamphetamine sulfate is approximately one and a half to two times as active as the racemic compound and three to four times as active than the levocompound. The stimulation of the central nervous system induced by these compounds is useful in the treatment of dizziness in certain patients. MICHAELS, Boston.

THE CONTROL OF NORMAL AND "CONVULSIVE" BRAIN POTENTIALS. R. W. GERARD and B. LIBET, Am. J. Psychiat. **96**:1125, 1940.

Gerard and Libet found that removal of the brain in the frog, while not changing the cortical frequency, increased the amplitude and regularity of the potentials. This they attributed, in part at least, to the absence of afferent impulses. On removal of the olfactory bulb repetition of definite potentials was found. These potentials are essentially those of the individual neuron. Deprivation of oxygen leads to obliteration of these potentials. Rise in temperature increased their frequency, amplitude and regularity. The authors point out that the regularity of the rhythm depends on the existence of a driving force and an interrupting mechanism. They studied factors involving control of metabolism and noted that anoxemia or narcosis, when impairing oxidation, abolished brain potentials. Cyanide, while acting similarly on the mammalian cortex, gave in the frog the peculiar response of abolition of potentials when the cortex was returned to Ringer's solution. Isolated frog brain was found to be indifferent to the absence of dextrose. Sodium iodoacetate gave rise to regular spikes, and this response could be removed by sodium lactate. Nicotine resulted in decreased frequency, increased amplitude and a sinusoidal type of wave. Sodium iodoacetate eliminated the nicotine response.

Factors concerned in the trip mechanism were then studied. Increasing osmotic pressure was found to cause large slow waves. Replacing intercellular salts or substituting sodium had a similar action. The ions which act on the cell membranes were found to produce sudden and discontinuous effects. An ascending current (olfactory bulb to occipital lobe) produced depression or abolition of potentials in the bulb, and this was followed by a period of increased activity. A descending current produced the converse state.

On considering the mechanism of cell synchronization, Gerard and Libet point out the necessity of a pace-making cell or group of cells. The transmission of impulses can be either along anatomic pathways or over electrical fields. The latter depends on the intensity of the force at its origin, the distance and intensity of its spread and the sensitiveness of the recipient units. Two criteria of the integrating mechanism are that the regularity of the potentials and the difficulty in disrupting the waves are in direct proportion to the strength of the integrating mechanism.

Mechanisms which increase membrane polarity increase the driving potential. Of these, caffeine was chosen and applied to an isolated brain. Gerard and Libet showed that caffeine waves continue to spread in the isolated brain when neural transmission is excluded. This was done by using nicotine to block synaptic transmission, transecting the brain and placing the halves in apposition. Finally, when two brains were placed in contact, one caffeinized and the other not, the characteristic waves were found in both.

FORSTER, New Haven, Conn.

EXPERIMENTAL STUDIES ON HEADACHE: PAIN-SENSITIVE STRUCTURES OF THE HEAD AND THEIR SIGNIFICANCE IN HEADACHE. BRONSON S. RAY and HAROLD G. WOLFF, Arch. Surg. **41**:813 (Oct.) 1940.

In the course of a comprehensive inquiry into the causes of headache, Ray and Wolff tested out the sensitivity of the extracranial and intracranial structures to pain. A variety of stimuli were used. All the tissues covering the craninum, especially the arteries, are sensitive to pain. The cranium, including the diploic and emissary veins, the parenchyma of the brain, most of the dura, most of the pia-arachnoid, the ependymal lining of the ventricles and the choroid plexuses, are not sensitive to pain. The great venous sinuses and their venous tributaries from the surface of the brain, parts of the dura at the base, the dural arteries and the cerebral arteries at the base of the brain are sensitive to pain. Stimulation of the pain-sensitive structures on or above the superior surface of the tentorium cerebelli resulted in pain in various regions in front of a line drawn vertically from the ears across the top of the heead. The pathways for this pain are contained in the fifth cranial nerve. Stimulation of the pain-sensitive intracranial structures on or below the inferior surface of the tentorium cerebelli resulted in pain in various regions behind the line just described. The pathways for this pain are contained chiefly in the ninth and tenth cranial nerves and the upper three cervical nerves.

From the data available, six basic mechanisms of headache have been formulated. Headache may result from (1) traction on the veins that pass to the venous sinuses from the surface of the brain and from displacement of the great venous sinuses, (2) traction on the middle meningeal arteries, (3) traction on the large arteries at the base of the brain and their main branches, (4) distention and dilatation of intracranial and extracranial arteries, (5) inflammation in or about any of the pain-sensitive structures of the head and (6) direct pressure by tumors on the cranial and cervical nerves containing many pain-afferent fibers from the head. Intracranial diseases commonly cause headache through more than one of these mechanisms and by involvement of more than one pain-sensitive structure. Traction, displacement, distention and inflammation of cranial vascular structures are chiefly responsible for headache. Headache from intracranial disease is usually referred pain. Local tenderness of the scalp may serve as an index to the structures responsible when a lesion produces direct irritation of pain-sensitive structures. Since disease of remotely separated pain-sensitive structures may cause pain and hyperalgesia in identical areas, the clinical usefulness of such localization is limited. But unilateral hyperalgesia localized in the parietal area indicates the possibility of a lesion near the middle meningeal artery, and hyperalgesia localized to the postauricular region indicates the possibility of a lesion in the region of the internal auditory meatus.

GRANT, Philadelphia.

MOVEMENTS ELICITED FROM PRECENTRAL GYRUS OF ADULT CHIMPANZEES BY STIMULATION WITH SINE WAVE CURRENTS. MARION HINES, J. Neurophysiol. **3**:442 (Sept.) 1940.

The precentral gyri of 3 adult chimpanzees were explored with the 60 contractions per second sine wave current. The movements elicited were interpreted as activation (*i*) of discrete motor nuclei of the cranial and spinal nerves and of parts of these nuclei; (*ii*) of groups of motor nuclei within the spinal cord which innervate extensor or flexor sheets of skeletal muscles, and (*iii*) of brain stem integra-

tion system. Certain of the coinnervations suggest cortical selection of nuclear groups, such that use patterns were elicited.

The most frequently elicited movements of skeletal muscles were those of the digits: flexion of the lateral four and adduction of the first. Isolated movements of the second or the fifth finger were rare; those of the third and fourth fingers did not occur. Different loci for antagonistic movements at the joints were obtained.

Vocalization, a light whistle and salivation were produced in 1 chimpanzee. The postcentral gyrus responded without previous facilitation.

The liminal strength of the stimulating frequency for area 4 (arm and leg) was higher (0.22 to 2.0 milliamperes) than for the face area (largely area 6) (0.2 to 1.5 milliamperes).

A single point on two of these precentral gyri was stimulated with a range of double vibrations (5 to 1,440 contractions per second) of sinusoidal current. Ninety contractions per second was the optimum frequency for each of these points. The frequencies eliciting movements which in their timing, sequence and smoothness resembled characteristics of the unanesthetized animal were those in the neighborhood of the optimum.

ALPERS, Philadelphia.

Neuropathology

SPINAL EPIDURAL ABSCESS ASSOCIATED WITH ACTINOMYCOSIS. NEWTON KRUMDIECK and LEWIS STEVENSON, Arch. Path. **30**:1223 (Dec.) 1940.

Spinal epidural abscesses are most frequently associated with Staphylococcus. Streptococcus is the next most frequent cause. Pneumococcus, the typhoid bacillus, Bacillus pyocyaneus and Oidium coccidioides have been reported as causative agents in isolated cases. Abscess due to actinomycosis has only rarely been reported. The authors report a case of such a condition in a 54 year old man in which a diagnosis of Hodgkin's disease had been made by biopsy ten years previously. Sudden paraplegia developed, with motor and sensory symptoms at the midthoracic level.

The anatomic diagnosis was actinomycosis with pneumonia and multiple pulmonary abscesses, osteomyelitis of the first and second ribs on the right and of the fourth, fifth and sixth thoracic vertebrae, with erosion into the spinal canal and formation of an epidural abscess, and abscesses of the liver.

WINKELMAN, Philadelphia.

DEATH FROM COMPLICATIONS OF METRAZOL TREATMENT. J. M. NIELSEN and SAMUEL D. INGHAM, Bull. Los Angeles Neurol. Soc. **5**:130 (June) 1940.

Nielsen and Ingham report the case of a psychotic woman aged 33 who while in the sitting position with thighs and spine flexed was given an intravenous injection of 5 cc. of a 10 per cent solution of metrazol. In the ensuing convulsion an intracapsular fracture of both femurs was produced. Cyanosis requiring oxygen persisted for nineteen hours; writhing movement appeared in the upper extremities with pathologic plantar responses bilaterally, and the patient died four days after the treatment. Autopsy revealed patchy bronchopneumonia and extensive multiple fat embolism of the brain.

MACKAY, Chicago.

AGENESIS OF THE CORPUS CALLOSUM ASSOCIATED WITH PORENCEPHALY. E. HAROLD SHRYOCK, JAMES F. BARNARD and ROBERT S. KNIGHTON, Bull. Los Angeles Neurol. Soc. **5**:146 (Sept.) 1940.

In the case described by Shryock, Barnard and Knighton, the multiparous mother of the patient exhibited transient vaginal bleeding at the eighth month of pregnancy, but delivered an apparently normal male infant at full term. The child had bronchopneumonia when 6 weeks old. Extensor spasms and a rash over the face and neck appeared when he was 3 months old, and persisted. He never sat

up. Neurologic examination at 9 months of age revealed that the child was mentally retarded, unresponsive and apparently blind; the pupils reacted to light. There was no paralysis, but the knee jerks were hyperactive. The head was normal in size and the neck retracted. The leukocyte count was 24,950; the Kahn and Kline reactions were negative, as had been the mother's during pregnancy. The child died, at the age of 9 months, with a carbuncle on the neck and an abscess of the lung.

Autopsy revealed a large porencephalic cavity in each frontoparietal area, with complete absence of the corpus callosum, septum pellucidum and hippocampal commissure. Thus, a large opening extended through the cerebrum from one side to the other. The roof of the third ventricle was missing, and this cavity communicated with a midline arachnoid cyst. Microgyria was present around the margins of the porencephalic openings; the sulci on the medial surfaces of the hemispheres were radially disposed; the parieto-occipital and calcarine sulci were separated on the right side; the optic nerves were small; aberrant masses of cortical tissue were observed beneath the ependyma over the basal ganglia, and the subcortical white matter was greatly reduced in amount. Along the dorsal margin of the porencephalic cavity of the right hemisphere was a sickle-shaped fasciculus the fibers of which had their origin in the parolfactory areas of both hemispheres and terminated in the hippocampal gray matter of the temporal lobes. Microscopically there were no evidences of softening, but round cell infiltrations were seen, with proliferation of the meninges and ependyma. The pyramidal system seemed to be absent. The internal granular layer of the calcarine cortex was imperfectly laminated, and the ganglion cells of the lateral geniculate body were not arranged in laminas.

Shryock, Barnard and Knighton emphasize the disparity between the extreme anatomic defects and the slight clinical manifestations. They believe the arrest of development occurred at about the fourth fetal month and may have been due to a chronic inflammatory process at that time. Apparently, it was not due to vascular lesions, syphilis, trauma at birth or any postnatal infection.

MACKAY, Chicago.

CHRONIC PROGRESSIVE DEGENERATION OF THE SUPERIOR CEREBELLAR CORTEX (PARENCHYMATOUS CORTICAL CEREBELLAR ATROPHY). CYRIL B. COURVILLE and ARNOLD P. FRIEDMAN, Bull. Los Angeles Neurol. Soc. **5**:171 (Sept.) 1940.

Courville and Friedman report the case of a white woman who had had "spinal meningitis" when a baby, with inability to talk or walk thereafter until she was 12 years old. When 33 years of age she began to have choreiform movements and awkwardness of her hands, as well as an unsteady gait. During the next nine years she suffered from progressive ataxia and numerous falls. One year before her death from gastric carcinoma, at the age of 42, examination revealed slurred speech, uncertain gait, ataxia of all the extremities, a positive Romberg sign and a pendular knee jerk, but no nystagmus. At autopsy the essential neurologic lesion observed was diffuse, irregular atrophy of the folia of the superior surface of the cerebellum, with some generalized reduction in the size of the hemispheres. Microscopically, the Purkinje cells were nearly all absent in the involved areas, and the granular layer was reduced in cell content. The basket cells were well preserved. Most of the myelin was absent in the affected folia, but was normal elsewhere. There was no gliosis, but the leptomeninges were adherent to the cortex, particularly in the secondary sulci, which were occasionally obliterated. Superficially the meninges were thickened and vascularized. No infiltrations were present. The olives, dentate nuclei and cerebellar peduncles were grossly normal.

Courville and Friedman reject most of the theories proposed in explanation of this condition. They think that it is not a disease entity, but that is due rather to a combination of diverse factors which lead to anoxia, involving particularly the superior surface of the cerebellum, which is pressed against the tentorium. The Purkinje cells, being most sensitive to deprivation of oxygen, are first to be damaged and the cells of the granular layer next.

MACKAY, Chicago.

PATHOLOGICAL CHANGES IN THE FUNDUS OCULI IN TUBEROUS SCLEROSIS. M. TARLAU and H. MCGRATH, J. Nerv. & Ment. Dis. **92**:22 (July) 1940.

In tuberous sclerosis the fundus of the eye may present white, mulberry-shaped or gray, nodular tumors arising from the optic nerve or retina and retinal pigmentation varying from yellow or black spots to patterns suggesting retinitis pigmentosa. Tarlau and McGrath report the case of an Italian woman who exhibited mental deficiency, grand and petit mal seizures, adenoma sebaceum and a large tumor of the left kidney. At the age of 22, after three years of observation, she had no retinal tumor, but eight months later the left optic disk was partially obscured by a large white mass, measuring 2 by 3.5 disk diameters and elevated about 3 D. at its center. Encephalographic examination revealed cortical atrophy and reduction in the size of the left temporal horn. At necropsy only the eye could be examined. The tumor measured 5 by 5 by 1.25 mm., was cystic and invaded the optic nerve and the nerve fiber layer of the retina. It was composed of astrocytes, which were occasionally multinucleated and which produced a prominent fibrillary network.

MACKAY, Chicago.

AMYOTROPHIC LATERAL SCLEROSIS WITH PSYCHOSIS. SERGE ANDROP, Psychiatric Quart. **14**:818 (Oct.) 1940.

Androp reports a case of a 55 year old man who at the age of about 35 began to express ideas of infidelity and delusions of persecution. These ideas were present at the time of hospitalization. On admission the results of physical examination were normal. For six years after admission mental deterioration progressed, until the patient's death. Periodic irritability, assaultiveness and childishness occurred. As loss of interest, memory defects, untidiness and hallucinations appeared, the original delusions of persecution disappeared. With the mental deterioration the clinical features of amyotrophic lateral sclerosis developed. Death resulted from myocarditis.

At autopsy the changes in the spinal cord characteristic of amyotrophic lateral sclerosis were observed to be associated with slight subarachnoid hemorrhage in the upper portion of the cord. In the brain there were some congestion of the cerebral vessels and thickening of the meninges. The architectural arrangement of the cortical layers was disturbed in the frontal and parietal areas and to a lesser extent in the temporal region. There was loss of ganglion cells in layers 3, 5 and 6. Degenerative changes were seen in the cells. The Betz cells were markedly reduced in number. The case is reported as an instance of amyotrophic lateral sclerosis associated with organic psychosis in which changes in the central nervous system were found to account for both. In the majority of reports in the literature the psychosis is considered as structurally unrelated to the motor neuron disease.

SIMON, Worcester, Mass.

CEREBELLAR ATROPHY ASSOCIATED WITH ÉTAT MARBRÉ OF THE BASAL GANGLIA. R. M. NORMAN, J. Neurol. & Psychiat. **3**:311 (Oct.) 1940.

In the brain of a 33 year old man who demonstrated no clinical signs other than low grade idiocy and spasticity of the lower extremities autopsy revealed a rare combination of typical olivopontocerebellar atrophy and état marbré of the basal ganglia bilaterally. There were marked reduction in the size of the cerebellum, particularly of the lateral lobes, pronounced atrophy of the inferior olives and mild sclerosis of the pontile nuclei and their transverse fibers. The relatively moderate histologic changes in the atrophied regions suggested hypoplasia resulting from onset of the atrophy prior to the full development of the cerebellum. The marble state involved the caudate nucleus, the putamen and the thalamus, the pallidum showing some demyelination. The unusual feature of the case was the absence of clinical signs referable either to the cerebellar or to the striate disorder. Hereditary trends were lacking, and the cause of the condition remained obscure.

MALAMUD, Ann Arbor, Mich.

NEUROANATOMIC EXAMINATION OF THE BRAIN AFTER LIGATION OF THE CAROTID ARTERY IN A CASE OF PULSATING EXOPHTHALMOS. J. CAMMERMEYER, Nord. med. (Norsk mag. f. lægevidensk.) **7**:1283 (July 27) 1940.

Cammermeyer's examination in the first of Schie's cases of pulsating exophthalmos showed a considerable degenerative process in the left hemisphere, limited to the cortex within the motor area and the adjacent convolutions. The cellular changes were of the "severe" (Nissl) and the "homogenized" (Spielmeyer) type. The glia cells in part showed regressive changes with pyknosis and karyorrhexis and in part milder "progressive nuclear changes." The author concludes that after the ligature of the carotid artery on the left side considerable necrosis of the cortex, ascribed to a probable embolic process, occurred corresponding to the end branchings of the middle cerebral artery. In the intensity and nature of the changes and their limitations the case resembles the cases of Müller and Döring, but it differs from them in that the pathologic changes are electively cortical, without involvement of the white substance or the basal ganglia. The onset of symptoms after an interval following the operation also suggests an embolic pathogenesis.

J. A. M. A.

Psychiatry and Psychopathology

PSYCHIATRIC APPROACH TO THE TREATMENT OF EPILEPSY. STANLEY COBB, Am. J. Psychiat. **96**:1009, 1940.

Cobb classifies epilepsy under two types: (*a*) the inherited cerebral dysrhythmias, which include the subclinical and the clinical forms, whether or not precipitated by a cerebral lesion, and (*b*) epilepsy accompanying a cerebral lesion without inherited dysrhythmia. He then defines epilepsy as a disorder of the brain causing repeated fits in which the usual functional abnormalities are electroencephalographic changes, partial or complete loss of consciousness and nervous discharge causing involuntary visceral or motor behavior. He then distinguishes between epilepsy and hysteria and advocates abolition of the term "hysteroepilepsy."

He reviews the results of intensive treatment of 45 patients. Psychologic therapy consisted of social corrective and social constructive measures, psychiatric interviews and psychoanalysis. Drug therapy consisted of administration of phenobarbital, bromides and dilantin sodium. Special measures included surgical procedures, administration of azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate) and ketogenic diet.

In all but 1 of Cobb's cases social and psychiatric measures were employed, but in only 2 instances was psychotherapy the only form of therapy. The frequency of seizures was increased in 7 cases, not appreciably changed in 6 and definitely decreased in the remaining 33. Improvement in personality was noted in 30 cases. Of those patients treated largely by psychotherapy, 67 per cent were markedly improved. Cobb advises, therefore, that the therapy of epilepsy be directed along numerous lines.

FORSTER, New Haven, Conn.

DEMENTIA PARALYTICA ACCOMPANIED BY MANIC-DEPRESSIVE AND SCHIZOPHRENIC PSYCHOSES. D. ROTHSCHILD, Am. J. Psychiat. **96**:1043, 1940.

Rothschild reports 5 cases in which dementia paralytica was associated with manic-depressive and schizophrenic psychoses. The first case is that of a woman presenting clinical features of both a hypomanic state and an organic psychosis. Laboratory studies confirmed the diagnosis of dementia paralytica. Malarial and tryparsamide therapy resulted in clearing of the spinal fluid and of the clinical features of an organic psychosis, but the hypomanic state persisted until death. Rothschild concludes that the hypomanic state and the dementia paralytica were two separate entities. The second patient had a manic psychosis with changes in the spinal fluid indicative of dementia paralytica. The psychosis cleared under malaria therapy, but there have been several subsequent manic attacks in a period of ten years. The illness of the third patient began with a depressed state; a

manic episode occurred, and then an organic psychosis, proved to be dementia paralytica, developed, to which he succumbed. Patients 4 and 5 first had a definite organic psychosis, were shown to have dementia paralytica and were treated accordingly, but retained psychoses of the schizophrenic pattern.

Rothschild concludes that there are cases in which a concomitant psychosis exists but remains undetected because of the organic disturbance, and he points out that released patterns of behavior may be regarded as part of the organic cerebral disease. It is possible that the therapy may eliminate or diminish the organic features, thus allowing the concomitant psychosis to become more evident.

FORSTER, New Haven, Conn.

A CASE OF PARTIAL BILATERAL FRONTAL LOBECTOMY. IRA C. NICHOLS and J. MCVICKER HUNT, Am. J. Psychiat. **96**:1063, 1940.

Nichols and Hunt report a case of a white man aged 45 with onset of developing anosmia and petit mal seizures in 1922, visual difficulty in 1928, personality changes in 1930 and, following this, impairment of memory. In 1934 he was hospitalized, and an olfactory groove meningioma was removed in two operations, during the course of which the anteroinferior portions of both frontal lobes had to be removed. Because of his psychiatric status institutionalization was necessary. The irritability and petit mal seizures subsided over a period of three years. The patient now requires routine care, is automatic and stereotyped in his activities and avoids making choices. Psychometric examination showed intelligence quotients between 118 and 122. Babcock tests gave evidence of some loss of ability, although his previous level was unknown. The Knox cube test showed marked deficit. The standard tests for deficit due to cerebral damage showed adequate immediate memory, failure to use the abstract attitude and inability to shift between the concrete and the abstract. The chief deficiencies which these tests outlined were (1) retention of a hypothesis that failed, (2) trying unplanned placements and (3) failure to appreciate the total system. Tests especially designed for the patient showed (1) failure to devise variations of technic after failure, (2) failure to profit from errors, (3) failure to search for new methods to attack a problem and (4) inability to sustain several parallel lines of activity separately.

FORSTER, New Haven, Conn.

PSYCHOSES WITH MYXEDEMA. RALPH M. CROWLEY, Am. J. Psychiat. **96**:1105, 1940.

Among 4,500 admissions Crowley found 2 cases of psychosis with myxedema. The first case was that of a woman aged 38 who, in addition to physical symptoms of myxedema, showed defect in judgment, preoccupation, periods of irritability and paranoid delusions. The basal metabolic rate was —38 per cent. Thyroid medication for two months resulted in recovery. Twice subsequently she ceased taking thyroid, and on both occasions the psychosis returned, each time disappearing again with thyroid treatment. The second patient was a widow aged 65 who for four years had undergone changes in personality. On admission she was restive, critical and suicidal and had a memory defect. General physical signs of myxedema were present. The basal metabolic rate was —20 per cent. Seven months of hospitalization without thyroid medication resulted in recovery.

Crowley points out that the picture of the psychosis itself is not specific for the disease but reflects the personality development of the patient. The importance of endocrine interrelationships is stressed.

FORSTER, New Haven, Conn.

HEREDITARY AND ENVIRONMENTAL FACTORS IN THE CAUSATION OF MANIC-DEPRESSIVE PSYCHOSES AND DEMENTIA PRAECOX. HORATIO M. POLLOCK and BENJAMIN MALZBERG, Am. J. Psychiat. **96**:1227, 1940.

Pollock and Malzberg studied the records for the first admissions of 155 manic-depressive patients and 175 schizophrenic patients. They obtained and verified

statements as to mental health of the patient's family, the developmental history of the patient and a description of the home life. This material was analyzed, first, by correlating the observations with mendelian laws and, second, by studying the differences in hereditary factors between psychotic and normal groups. Among the manic-depressive patients it was not possible to obtain data in agreement with mendelian requirements. The actual total of schizophrenic as well as of manic patients was far less than that computed by mendelian methods.

Pollock and Malzberg conclude that no specific law of inheritance of mental illness is proved, but that a familial basis is probable. The actual development of a psychosis, however, requires the addition of some factor to the predisposition. Two such factors to be considered are personality and environment. In both manic-depressive and schizophrenic patients exciting personality trends were brought out. The exciting factors in the two groups were not dissimilar.

FORSTER, New Haven, Conn.

HABITUS AND PERSONALITY IN MENTAL DISEASE ASSOCIATED WITH ORGANIC DISEASE. EUGENE DAVIDOFF, GERALD L. GOODSTONE and EDWARD C. REIFENSTEIN JR., Psychiatric Quart. **14**:809 (Oct.) 1940.

The authors analyzed a series of 100 cases representing consecutive admissions to a psychopathic hospital in which the diagnosis was psychosis with organic disease and in which the psychosis developed only after the onset of the organic illness. The organic diseases included infectious diseases, postinfectious states, somatic disease and toxic, metabolic and endocrine disturbances. The psychiatric symptoms were apathy, depression, homicidal and suicidal trends, agitation, destructiveness, assaultiveness, impulsiveness, delusions, hallucinations, confusion and delirium.

Ninety-one per cent of the patients had disorders of the prepsychotic personality. Thirty-four per cent had a dysplastic and 14 per cent a pyknic habitus. The patients with a pyknic habitus showed a higher percentage of balanced personalities than those with the dysplastic type. The psychotic patterns and content were found to be related to the personalities of the patients.

This series was compared with a series of severely neurotic or psychotic patients studied in a general hospital. Less than half of the latter showed poor adjustment to hospital or home. The percentage of patients of the dysplastic type was definitely lower, and that of patients of the pyknic type was higher. Patients of asthentic type constituted about half of both series. Again, in the second series the patients of pyknic type showed a higher proportion of good premorbid personalities (82 per cent). Psychotic manifestations in the second series were milder and appeared less dependent on the premorbid personality. Differentiation between organic and functional psychoses was easier than in the first series, though psychoneurotic symptoms presented more diagnostic difficulties.

SIMON, Worcester, Mass.

A CONTRIBUTION TO THE PSYCHOANALYSIS OF EXTREME SUBMISSIVENESS IN WOMEN. ANNIE REICH, Psychoanalyt. Quart. **9**:470, 1940.

The woman who shows extreme submissiveness is one who finds life impossible without a partner and who is willing to comply with all the partner's wishes even if such compliance means the sacrifice of her own interests, independence, self reliance and self esteem. She overvalues her partner and sexual relations and has a feeling of bliss during orgasm which is beyond any true orgastic sensation. Reich considers this behavior to have the characteristics of a perversion. The ecstasy during orgasm is a defense against deep feelings of anxiety, despair and helplessness which are experienced when the woman is separated from her love object. Her self esteem becomes low when she is away from her love because she has renounced her own narcissism and projected it onto the man, which results in his being overvalued. The pattern is based on such infantile ideas

as that a woman in intercourse will get a penis and retain it; that a woman has to be castrated and destroyed in order to be loved and made whole (a masochistic reaction), and that because a girl has no penis she is inferior, a trauma, which accentuates her desire for male attention and love, in the hope that it will bring her a penis. There likewise exist in the deeper levels of the mind a childish fixation to the mother and, at the same level, the idea that an orgasm means a mystic fusion with the mother. This is necessary in order to keep repressed the intense hostility toward the mother.

In actual life, as long as her love affair works her basic hostility to the man, transferred onto him from her mother, is neutralized by the erotic act. In brief, the submissive woman masters her relentless destroying attitude to her mother by repression, an attitude which is later transferred onto the man. Such women show basically complete intolerance of any frustration. They would like to act in the presence of frustration as a baby does, but they conform to the reality principle, to the need of emotional continuity and to the necessity of minimizing mood swings by a narcissistic elevation of the object, by the pleasure gratification of the ecstatic love expression and by the transformation of aggression into masochistic behavior.

PEARSON, Philadelphia.

HEADACHE AS AN EARLY SYMPTOM OF NERVOUS AND MENTAL DISORDER. D. CURRAN, Brit. M. J. **2**:717 (Oct. 7) 1939.

Curran states that there is an increasing tendency to consider some headaches as of psychotic origin. Sprigg found that of 500 cases in which headache was the chief complaint, the origin was functional in 203. The author believes that whether or not a headache is a psychiatric problem depends on whether it can be attributed directly to impersonal physical factors or whether it is the result of disorders of the personality as a whole.

Headache or head discomfort is subjectively experienced when there is a threat to the personality or an upset of the sense of well-being. The psychiatric headache is characteristic of the personality of the sufferer. The typical feature of psychiatric headache is the subjective experience of the quality of what might be called "closeness," as opposed to "remoteness," to the personality. The functional headache is typified by an unpleasant experience with a special personal significance, whereas the organic headache is characterized by a sensory perception which is not germane to a personal attitude of the patient. The functional headache is a selective disturbance of function, usually diffuse in location but sometimes frontal, which is influenced by psychologic events. Included among the associated conditions that should suggest that a headache is part of a psychiatric syndrome are schizophrenia, organic reactions, affective reactions, anxiety and hysteria. Functional headaches have been considered by some to be dependent on the results of the physiologic changes accompanying emotional disturbance.

ECHOLS, New Orleans.

METHOD OF FABLES IN PSYCHOANALYSIS. L. DÜSS, Arch. de psychol. **109**:1, 1940.

A method of psychoanalysis is presented especially for use by those who work with children and is designed to reveal the complexes underlying certain types of abnormal behavior. Ten short stories were made up, each one to fit a different complex or character difficulty, such as parent fixation or the castration complex, and these stories were told to the subjects. After each story pertinent questions were asked. Symbolic responses or resistance to certain questions indicated complexes and repressions. Of the 65 subjects tested (43 children and 22 adults), 14 had a known neurotic background. The validity of the test was established by the correspondence of the responses of these 14 neurotic subjects to their known complexes. The author says that the method of fables reveals quickly and clearly the complexes of children and has a limited applicability to adults.

SHURRAGER, Philadelphia.

LOSS OF IDEAS. E. CLAPARÈDE, Arch. de psychol. **109**:59, 1940.

Claparède calls the attention of psychologists to the complete and inexplicable loss of ideas which is more frequent with advancing age. The lost idea, even though it is one of particular interest to its originator, never recurs spontaneously to memory. The loss seems to have no affective genesis, since writing the idea down, though it abolishes the fear of its being lost, does not prevent the forgetting. Moreover, fear of forgetting cannot explain the original loss of ideas. No theory of memory satisfactorily accounts for the facts. The phenomenon of the loss of ideas, together with evidence from the histories of famous inventions, leads the author to conclude that good ideas occur largely as the result of psychologic chance.

SHURRAGER, Philadelphia.

Meninges and Blood Vessels

ARTERITIS OF THE TEMPORAL VESSELS. JAMES M. BOWERS, Arch. Int. Med. **66**:385 (Aug.) 1940.

Bowers describes an inflammatory process of unknown origin which selectively involves the temporal arteries and differs from thromboangiitis obliterans, periarteritis and rheumatic arteritis. The medial coat is first attacked with production of areas of necrosis, which are later replaced by granulation tissue containing numerous giant cells. All coats may be involved, resulting in intimal thickening and adventitial round cell infiltration with extension into healthy tissues. The lumen of the vessel may be closed by thrombi.

Agglutination tests, cultures and special stains have failed to reveal any definite causative agent. The disease affects both sexes, usually after the age of 60, and often occurs in persons with hypertension and arteriosclerosis. The illness lasts about six months and eventually subsides completely. The outstanding complaint is a dull, throbbing headache, which is worse at night. Fever, anorexia, loss of weight, weakness, anemia and leukocytosis also may be present. Later the temporal vessels become enlarged and tortuous and are surrounded by areas of hyperemia. Small nodules may be felt over the vessel, and the pulsation may be diminished or absent. Fifteen cases have been reported in the literature since the condition was first described in 1931.

There is no specific treatment for the disease, but in the case reported resection of a small segment of the anterior branch of the left temporal artery and large doses of vitamin B_1 produced relief. The patient had suffered from hypertension and severe head pain for a considerable period. Nine months after the cessation of all signs and symptoms she had a cerebral ictus. The most likely cause of this accident, according to the author, was arteritis of the cerebral vessels of a similar nature to that found in the temporal vessels.

It is suggested that the 16 cases now on record represent a distinct type of arteritis, especially distinct from periarteritis nodosa.

BECK, Buffalo.

TRAUMATIC INTRACEREBRAL HEMORRHAGE, WITH PARTICULAR REFERENCE TO ITS PATHOGENESIS AND ITS RELATION TO "DELAYED TRAUMATIC APOPLEXY." CYRIL B. COURVILLE and OLOV A. BLOMQUIST, Arch. Surg. **41**:1 (July) 1940.

In order to evaluate Bollinger's conception of delayed post-traumatic apoplexy, a study was made of 38 cases of gross hemorrhage into the brain substance occurring as the direct result of trauma. Except for 3 cases of gross hemorrhage resulting from direct laceration of the brain, a traumatic hemorrhage proved invariably to be a typical *coup-contrecoup* effect of injury, in which the head in motion struck an immobile, or relatively immobile, object. Two varieties of traumatic intracerebral hemorrhage are described. The first type is adjacent, or secondary, hemorrhage, which is a part of a contusion of the temporal and frontal lobes which provokes it and is of no special clinical significance. The second variety is primary, or central, hemorrhage occurring in the centrum of the frontal or temporal lobes

(rarely, in the less extensive form, in the external capsule and the ventricular nucleus). Central hemorrhages of the frontal and temporal lobes may reach such proportions as to assume clinical importance. Such hemorrhages, particularly those occurring in the temporal or temporo-occipital centrum, become manifest clinically after an interval of lucidity or may pursue a progressive course in a patient who has never been rendered entirely unconscious. In such cases the clinical course mimics closely that of interval dural hemorrhages. When such hemorrhages are excessive, ultimate rupture into the ventricles or into the subdural space seems to be the rule. In the latter instance these subdural accumulations of blood may be mistaken for primary subdural hemorrhages. Hemorrhages into the region of the basal ganglia following trauma apparently are limited to small extravasations occupying slitlike cavities in the external capsule or to small globular hemorrhages into the globus pallidus. No example of gross hemorrhage into the posterior limb of the internal capsule, such as appears spontaneously in cases of hypertension or arteriosclerosis, has been observed by the authors. It may, therefore, be safely assumed that gross hemorrhage in this region is not the result of trauma, for, of all portions of the brain presenting evidences of injury, this particular region seems to be most notably free. Arteriosclerosis in itself does not seem to play an important part in the production of traumatic hemorrhages, although it may have a mild predisposing influence. There seems to be no greater incidence of gross intracerebral hemorrhage in persons with advanced arteriosclerosis and associated severe injuries than in younger adults. Other, rarer conditions, such as hypoplasia of the arteries or other vascular disease, may play a minor role in the production of post-traumatic hemorrhages. Syphilis seems to be of no influence whatever as a predisposing factor in the production of immediate or delayed hemorrhages.

GRANT, Philadelphia.

EVIDENCE OF FOCAL VASCULAR DISTURBANCE IN MIGRAINE EQUIVALENT. J. M. NIELSEN and SAMUEL D. INGHAM, Bull. Los Angeles Neurol. Soc. **5**:113 (June) 1940.

Nielsen and Ingham report 5 cases of migraine, in each of which so-called equivalent attacks occurred suggesting focal cerebrovascular changes. In the first 2, migraine attacks were interspersed with confusional episodes characterized by spatial disorientation, a symptom which results from a lesion of Brodmann's area 19 and hence is attributable to interference with the circulation of the posterior cerebral artery. In the third case attacks of migraine were replaced at the menopause by periods of emotional exhilaration and confusion, with trembling, slurred speech, amnesia and uncertainty of gait without headache. Here a disturbance of circulation in the thalamic and subthalamic region is suggested. In the fourth case a woman who had had attacks of teichopsia for years began to have periods of confusion with loss of association of auditory and visual images, suggesting vascular disturbance in the posterior associational area of Flechsig. The fifth case was a less clear instance of temporary interference with consciousness and a measure of automatism in a sufferer from migraine. Nielsen and Ingham think that a separation of the thalamus from the cerebral cortex might produce such a condition, possibly from a disturbance in both anterior choroidal arteries.

MACKAY, Chicago.

FURTHER EXPERIMENTS ON THE REGENERATION OF END-ARTERIES IN THE BRAIN OF THE OPOSSUM. ERNST SCHARRER, J. Exper. Zool. **85**:365 (Dec.) 1940.

Two types of vascular patterns are known to exist in the brains of vertebrates, one in which the capillaries form an anastomosing network and the other in which the capillaries do not anastomose but end in slender loops. The reticular pattern has been found in all Placentalia among the mammals thus far studied, while the second pattern has been found in two species of the Marsupialia, the opossum and the kangaroo. The problem arises whether the factors that determine the type of

vascular pattern exist in the structure of the brain or in the cerebral vascular system itself. Reciprocal exchanges of brain implants between the rat, the guinea pig and the opossum were carried out. The blood vessels in brain tissue of the opossum regenerated as terminal capillary loops not only when they penetrated implanted opossum brain tissue, but also when they penetrated implanted brain tissue of the rat or the guinea pig. It is concluded that the pattern of the opossum's cerebral vessels is not forced on them during regeneration but is independent of any chemical or structural factor inherent in the brain tissue.

WYMAN, Boston.

THE CAPILLARY BED OF THE CENTRAL NERVOUS SYSTEM OF DERMOPHIS (AMPHIBIA, GYMNOPHIONA). E. HORNE CRAIGIE, J. Morphol. **67**:477 (Nov.) 1940.

Previous studies have shown that there is a clearcut morphologic difference in the capillary bed of the central nervous organs in two orders of amphibians, the Caudata and the Salientia. In the latter it is a continuous network, while in the Caudata it consists of slender, independent loops extending inward from the surface and not anastomosing at all. Since the Gymnophiona are believed to have retained may primitive characteristics and are probably the nearest living representatives of the first terrestrial vertebrates or of the immediate ancestor of the reptiles, a study of the brain of Dermophis mexicanus was undertaken. The material consisted of three series of sections, two from larvae and the other from an adult. It was found that all parts of the brain and the upper end of the spinal cord are vascularized by slender capillary loops similar to those of the Caudata. This supports the view that the cerebral capillary bed consisting of slender loops is the more primitive pattern and that the primitive Labyrinthodontia, the nearest common ancestors of living amphibians and of the reptiles, may have had cerebral vessels of this type. This implies that the reticular type of capillary bed must have appeared independently at least four times in submammalian vertebrates, since it is present in some cyclostomes, in fishes, in the Salientia and in some reptiles.

WYMAN, Boston.

THE VASCULAR COMPLICATIONS OF CERVICAL RIBS AND FIRST THORACIC RIB ABNORMALITIES. KENNETH C. EDEN, Brit. J. Surg. **27**:117 (July) 1939.

Many who have written on cervical ribs have neglected to discuss the vascular anomalies associated with this condition, but Eden has reported on these in detail. In the majority of cases of vascular involvement pain is sooner or later experienced in the arm. It differs markedly from the pain in cases of nerve involvement, which is lancinating and shoots down the arm into the fingers. It is influenced considerably by posture, being provoked by carrying heavy articles in the hand or by relaxing the shoulders in an armchair or bed. In cases of vascular disturbance there is a characteristically cramplike pain in the muscles of the forearms, which is sometimes absent during rest but which comes on rapidly during use of the arm. When the muscles are tender the pain may take some minutes to wear off after vigorous exercise. In the latter case the pain is not of neuralgic origin but is due to muscular ischemia. The vascular changes in the arm are caused by the cervical rib or its counterpart and by the damage to the subclavian artery with thrombus formation.

In the presence of compression of the subclavian artery from a cervical rib or its counterpart, the simplest procedure is removal of the cervical rib.

STUCK, Denver.

THE CAUSES OF RELAPSE FOLLOWING SYMPATHECTOMY OF THE ARM. H. T. SIMMONS and DONAL SHEEHAN, Brit. J. Surg. **27**:234 (Oct.) 1939.

Relapses after sympathectomy of the arm for Raynaud's and similar diseases are the result of a progressive fault in the digital vessels which overtakes and nul-

lifies the vasodilatation produced by the sympathectomy. This belief is supported by the frequent impossibility of demonstrating the presence of vasoconstrictor nerve fibers, and also by the rise in temperature of the skin following temporary ulnar nerve block many months after sympathectomy. Although there is some evidence of nerve regeneration in these cases, the most frequent cause of relapse is a local fault in the digital vessels.

STUCK, Denver.

PRIMARY DIFFUSE EPENDYMITIS. T. GERÉB and J. DÉNES, Confinia neurol. **3**: 115, 1940.

Geréb and Dénes describe the case of a man aged 57 in which signs of internal hydrocephalus and the clinical picture of a pseudotumor developed. Postmorten examination revealed the presence of a subacute inflammatory reaction affecting only the ependyma but involving the ependymal tissues in all the cerebral ventricles. They term the condition primary, diffuse ependymitis but suggest no etiologic factor.

DE JONG, Ann Arbor, Mich.

Diseases of the Brain

PERIPHERAL NEUROPATHY AND TOXIC PSYCHOSIS WITH CONVULSIONS DUE TO SULFAMETHYLTHIAZOLE. C. F. GARVIN, Am. J. M. Sc. **200**:362 (Sept.) 1940.

Garvin reports the case of a Negress aged 37 who had type XIV pneumococcus in both the sputum and the blood. An initial dose of 4 Gm. (60 grains) of sulfamethylthiazole (2-sulfanilamido-4-methylthiazole) was given, with 1 or 2 Gm. (15 or 30 grains) every four hours thereafter. The blood level of the sulfamethylthiazole averaged 36 mg. per hundred cubic centimeters. On the seventeenth hospital day there were tenderness and hyperesthesia of the legs, which were considered to be indicative of early peripheral neuropathy. On the eighteenth day the patient had two generalized convulsions, each of which lasted about three minutes, after which she became delirious and required restraint. During the following three days the patient had twelve generalized convulsions and died on the twenty-fourth day in the hospital. The brain was normal grossly and microscopically. Convulsions caused by sulfamethylthiazole have not been reported, and in this respect the case is noteworthy.

MICHAELS, Boston.

METHOD OF DIAGNOSING IDIOPATHIC EPILEPSY. F. C. DELORENZO, J. Pediat. **17**:355 (Sept.) 1940.

DeLorenzo employed the antidiuretic and superhydration test introduced by McQuarrie as a diagnostic aid in 17 cases of convulsions. The procedure is as follows: 1. A diet of 40 per cent cream and dextrose in antiketogenic proportions is given every six hours. 2. From 2 to 5 cc. of water per kilogram of body weight and an amount of pitressin sufficient to prevent diuresis are given at intervals of three to four hours. 3. The patient is weighed every six hours after the bladder is emptied and before food or water is taken. 4. A complete record is kept of the food, water and pitressin given and of the weight and urine. 5. A preliminary period of dehydration facilitates the occurrence of seizures. 6. The procedure is stopped when convulsions, symptoms of water intoxication (abdominal cramps, excessive vomiting and headache) or symptoms of pitressin toxicity occur or when it is evident that convulsions will not occur. All the requirements of the test must be fulfilled and kept under strict surveillance to prevent mistakes and frequent failure. Two of the 17 patients with convulsions had lead encephalopathy, 1 had convulsions following trauma to the head, 3 were less than 3 years of age, 1 had convulsions associated with an infection and pyrexia, 1 had petit mal and the others had conditions diagnosed as idiopathic epilepsy. With the exception of 2 patients, all with a diagnosis of idiopathic epilepsy reacted positively to the

McQuarrie test. Encephalograms made subsequent to the positive tests were negative. Of the 2 patients with negative reactions to the McQuarrie test, 1 was of a patient with hypoglycemia and in 1 the pitressin did not have the usual antidiuretic effect. The test was repeated a month later for the last patient and gave a positive reaction. Seventeen normal children who served as controls reacted negatively to the McQuarrie test. The child whose convulsions seemed to be precipitated by cerebral trauma gave a negative reaction to the test; subsequently an encephalogram indicated enlargement of the left ventricle. The other patients with convulsions and the patient with petit mal reacted negatively to the test. It is difficult to determine the true significance of the test from such a small group of patients, but the authors feel that there is sufficient evidence to justify employing it as an aid in differentiating idiopathic epilepsy from other conditions simulating it. Negative results will often lead to further investigation and the discovery of an entity which may be treated satisfactorily. They suggest that in idiopathic epilepsy there may be a disturbance in the normal physiologic mechanism in the cortical cell membranes and that any anatomicopathologic change found in these cases may have been the result, rather than the cause, of the disease.

J. A. M. A.

NEW ELECTRO-ENCEPHALOGRAPHIC RHYTHM IN EPILEPSY. T. DALSGAARD-NIELSEN, Nord. med. (Hospitalstid.) **6**:1119 (June 29) 1940.

Dalsgaard-Nielsen reports 3 cases of symptomatic epilepsy with a peculiar "1 Hertz rhythm" not previously described, which is characterized by (1) regularity, (2) low frequency ("1 Hertz rhythm"), (3) low potential, about like that of a normal fronto-occipital Berger rhythm, (4) typical form, with even slow rise and abrupt fall and (5) derivation from a single focus. In the first case there was evidence of cerebral atrophy at the site of the lead, but the history did not suggest traumatic origin. In the second a traumatic factor seemed possible, and there were clinical signs of pathologic changes in the brain at the site of the lead. In the last case, with certain traumatic origin, ventriculographic study and operation confirmed the presence of a traumatic brain process at the site of derivation. The author warns that there may be sources of error and that this rhythm may originate as a pulsation phenomenon, and says that evaluation of the nature and diagnostic importance of the "1 Hertz rhythm" must await the result of further examinations.

J. A. M. A.

Congenital Anomalies

KLIPPEL-FEIL SYNDROME. H. G. HADLEY, Virginia M. Monthly **67**:421 (July) 1940.

According to Hadley, the symptom complex of short neck, growth of the hair low down on the neck and limitation of head movements, which now bears the name of the Klippel-Feil syndrome, is found with congenital anomalies of the cervical portion of the spine. He presents 3 cases. The first patient, a man aged 48, was operated on at the age of 20, under a mistaken diagnosis of congenital torticollis. The deformity persisted. There were a marked cervicodorsal lateral curvature to the right and limitation of the head movements in all directions. Roentgen examination showed fusion of the second and third cervical vertebrae and incomplete development of the left half of the sixth, forming a wedge-shaped vertebra. There was an upright cervical rib. The second patient, a woman aged 37, was noted to have an abnormally short neck, with a low margin of the hair. She had considerable lack of motion of the neck, with the head tilted to the right. Roentgen examination showed that the first and second, as well as the fifth and sixth, cervical vertebrae were fused. There was also spina bifida occulta of the sixth and seventh cervical and first four thoracic vertebrae. The third patient, a woman aged 44, complained of pain in the left shoulder, which was higher and

closer to the vertebrae than the right. There was marked limitation of movement of the left shoulder. Roentgen examination showed a typical Sprengel deformity with articulation of the left scapula to the first, second and third thoracic vertebrae. Spina bifida occulta of the first, second and third thoracic vertebrae and scoliosis, with the convexity to the left, were present.

The typical Klippel-Feil syndrome is due to a numerical reduction of the cervical vertebrae. With this may be associated spina bifida anterior, which causes usually a cervical dorsal curve with the convexity generally to the left and with a sharp inflection at the summit. Spina bifida posterior usually causes an abnormal neck with inclination of the head to the side and elevation of the corresponding shoulder. An atloido-occipital fusion often presents a form resembling spasmodic torticollis if the disturbance is asymmetric, or Pott's disease if it is symmetric. In the clinical study the shortness of the neck bears a relation to the gravity of the malformation, and the head in severe deformities appears to repose directly on the trunk. A round back may be present, owing to the absence or alteration of the normal cervical curve. Accessory signs are scoliosis, disproportion of the length of the arms and of the trunk and low placement of the ears; there is ascension of the skeleton in relation to the skin. Elevation of the scapula is a striking accompaniment.

J. A. M. A.

Cerebrospinal Fluid

A Follow-Up Study of Non-Luetic Psychotic Patients with Abnormalities in the Spinal Fluid. Philip Solomon, Robert S. Schwab and Leo Maletz, Am. J. Psychiat. **96**:1035, 1940.

Solomon, Schwab and Maletz found among 12,000 psychotic patients 368 who demonstrated abnormalities of the spinal fluid not associated with syphilis. On 165 of these patients follow-up studies were made after an average period of thirty-four months. As a result of these studies the patients were divided into four groups: (1) those in whom the abnormal findings in the fluid were due to laboratory error; (2) those in whom organic disease was suspected and has since been confirmed (42 per cent); (3) those in whom organic disease was discovered by the follow-up studies (12 per cent), and (4) those in whom the abnormalities remain unexplained (42 per cent).

Solomon, Schwab and Maletz point out the prevalence of cerebral vascular disease in groups 2 and 3, in which 30 per cent of the patients were affected. Twenty-seven of the patients in these two groups had chronic alcoholism. The authors stress the importance of abnormalities of the spinal fluid in the presence of drug intoxication. They point out that in over half the cases comprising the report follow-up studies elucidated the cause of the abnormality. They point out that an abnormal colloidal gold curve is especially noteworthy.

Forster, New Haven, Conn.

Study of the Hemato-Encephalic Barrier by the Bromide Method, Before and After Insulin Therapy. M. M. Kessler, J. Nerv. & Ment. Dis. **91**:428 (April) 1940.

Kessler made a study of the permeability of the hematoencephalic barrier in 54 patients, using a modification of the Walter bromide method. Of these, 43 suffered from undoubted dementia praecox, 3 from psychosis with mental deficiency, 4 from psychosis with psychoneurotic coloring and 4 from affective psychosis. Permeability studies were made before and after insulin therapy. The results showed that the usual range of the quotient was from 2.0 to 4.0. There was, however, considerable variation, which suggested that the quotient is inversely representative of the permeability at the time of testing. No consistent change was noted as a result of insulin therapy, and no correlation could be established between the quotient and the type of dementia praecox, the blood pressure, the

basal metabolic rate or the physical habitus. A slight correlation between increased permeability and advancing age was suggested. There seemed to be a positive correlation between a low quotient (increased permeability) and increased psychomotor activity.

MACKAY, Chicago.

CHLORIDES IN THE CEREBROSPINAL FLUID. JOÃO BAPTISTA DOS REIS and HANS SCHMIDT, Arq. Serv. assist. psicopat. Estad. São Paulo **4**:337, 1939.

Reis and Schmidt used the technic of Mohr to study the chlorides in the spinal fluid. Normal values, varying from 702 to 755 mg. per hundred cubic centimeters of spinal fluid, were obtained in 1,500 cases. By adding varying amounts of blood to the spinal fluid the authors studied the effect of the presence of increased protein on the values for sodium chloride. Unless the total protein content is over 1 Gm. per hundred cubic centimeters, there is no need to deproteinize the fluid before making the chloride determination. In cases of starvation the chlorides may be diminished to 700 mg. per hundred cubic centimeters. Diminution of chlorides was found in association with the meningitides, especially the tuberculous type. When renal function is disturbed the values for chloride in the spinal fluid may use to 900 mg. per hundred cubic centimeters. In cases of dementia paralytica diminished chloride values indicate significant involvement of the meninges. Values near the upper limit of normal (760 mg.) indicate a favorable prognosis. If the chlorides are above 670 mg. per hundred cubic centimeters one should look for renal complications, perhaps secondary to prolonged treatment with arsenicals. In 900 readings on patients with neurosyphilis the values varied from 661 to 807 mg. per hundred cubic centimeters.

SAVITSKY, New York.

Treatment, Neurosurgery

INFLUENZAL MENINGITIS TREATED WITH SULFAPYRIDINE. J. H. ARNETT, G. D. SHOUP and N. W. HENRY, Am. J. M. Sc. **200**:674 (Nov.) 1940.

Arnett, Shoup and Henry report the case of a white girl aged 13 who had been deaf since she recovered from an attack of cerebrospinal meningitis, at the age of 7 years. Influenzal meningitis developed, and Pfeiffer's bacillus was recovered. Four hours after admission she was given 2 Gm. (30 grains) each of sulfapyridine and sodium bicarbonate, and thereafter, 1 Gm. of each of these drugs every four hours night and day. The patient recovered from the meningitis. Ten days after admission to the hospital examination of the abdomen revealed moderate hydronephrosis of the right kidney. There was bilateral ureteral obstruction, which is a well recognized complication of sulfapyridine therapy. The report emphasizes (1) the value of sulfapyridine in the treatment of influenzal meningitis, (2) its potentialities for damage to the upper portion of the urinary tract and (3) satisfactory recovery after complete ureteral blockage.

MICHAELS, Boston.

DELIRIUM TREMENS. M. ROSENBAUM, P. PIKER and H. LEDERER, Am. J. M. Sc. **200**:677 (Nov.) 1940.

Rosenbaum, Piker and Lederer review the results of treatment in 234 consecutive cases of delirium tremens. Three factors common to all cases were arbitrarily chosen as a basis of comparison: (1) the duration of the psychosis (average duration was 2½ days), (2) the length of stay in the hospital (average period of recovery was 5.3 days) and (3) the amount of paraldehyde used in each case. In 142 cases in which routine therapy and forcing fluids (3,000 to 4,000 cc. daily) were employed the average duration of illness was 4.75 days, while in a similar group of 142 cases in which the fluids were limited (less than 1,000 cc. daily) the average duration of illness was 4.65 days. In a group of 91 cases in which routine therapy plus digitalis was employed the average duration of the psychosis was 2.1 days, as compared with 2.3 days for a group of 59 cases in which no

digitalis was given. The average stay in the hospital of patients in the digitalized group was 4.3 days, as compared with 5 days for the nondigitalized group. The average amounts of paraldehyde given were 16 and 18 fluidrachms (59.13 and 66.53 cc.) respectively. In 86 patients given routine treatment plus dextrose the average duration of the psychosis was 2.6 days, as compared with 2.5 days for 107 patients given routine treatment plus sucrose. The average stay in the hospital was 5.3 days for the group receiving dextrose as compared with 5.7 days for the group receiving sucrose, and the average doses of paraldehyde were 15 and 20 fluidrachms (55.4 and 73.92 cc.) respectively. A comparison of 136 cases in which more than 21 cc. of spinal fluid was drained at one tap (average amount 40 cc.) and 73 cases in which less than 21 cc. was drained (average amount 13 cc.) shows that the average duration of psychosis for the groups was 2.6 and 2.7 days respectively, the average stay in the hospital 5.2 and 6 days and the average dose of paraldehyde 19 and 17 fluidrachms (70.32 and 62.63 cc.). In those cases of delirium tremens in which thiamine hydrochloride was given the average duration of the disease was 2.2 days, as compared with 2 days in a control group; the average stays in the hospital were 6.6 and 5.5 days, and the average amounts of paraldehyde used were 11.3 and 15 fluidrachms (41.74 and 55.44 cc.). From their experience, the authors conclude that the addition of thiamine hydrochloride, nicotinic acid, liver extract and brewers' yeast does not seem to aid in shortening the illness. In view of the similarity in results, regardless of the type of therapy used, the factors common to all of them included only length of hospitalization, dose of paraldehyde, lumbar puncture (some for drainage and some for diagnostic purposes) and the attitude of the staff toward the patients. Of these factors, the attitude seems particularly significant. The authors conclude that a specific therapeutic medicinal procedure for delirium tremens could not be found but that the place of psychotherapy in the treatment of this disease merits more consideration generally than it has received until now.

MICHAELS, Boston.

FURTHER EXPERIENCES WITH THE USE OF SODIUM DIPHENYL HYDANTOINATE IN THE TREATMENT OF CONVULSIVE DISORDERS. H. HOUSTON MERRITT and TRACY J. PUTNAM, Am. J. Psychiat. **96**:1022, 1940.

Merritt and Putnam reported the results of dilantin therapy in 267 ambulatory patients with epilepsy. All the patients had previously received other forms of treatment. The duration of dilantin therapy varied from two to twenty-two months. The ages ranged from 2 to 70 years, 84 per cent of the patients being between 10 and 50 years old. The duration of the illness varied from less than a year to over forty years. One hundred and sixty-four patients had but one type of seizure. Sixty-two per cent of 39 patients with psychomotor attacks were completely relieved. Of the 227 patients having grand mal attacks, 60 per cent were completely relieved and an additional 27 per cent were improved. Of 104 patients with petit mal attacks, 39 per cent were completely relieved and an additional 40 per cent were improved.

The dose of dilantin sodium varied from 0.2 to 0.6 Gm. per day. Institution of the treatment was by a process of gradual substitution for previous medication. The necessity in many cases of a dose higher than 0.3 Gm. per day is stressed.

Toxic manifestations included those referable to the gastrointestinal tract and the central nervous system. Dermatitis and hyperplasia of the gums were noted.

FORSTER, New Haven, Conn.

A COMPARATIVE STUDY OF THE EFFECTIVENESS OF DILANTIN SODIUM AND PHENOBARBITAL IN A GROUP OF EPILEPTICS. J. WEINBERG and H. GOLDSTEIN, Am. J. Psychiat. **96**:1029, 1940.

Weinberg and Goldstein reported the results of treatment of 15 patients with idiopathic epilepsy, ranging in age from 21 to 50 years, with a duration of the epilepsy of from six to thirty-eight years. The authors' method consisted of no

medication for one month, use of phenobarbital, 1½ grains (0.097 Gm.) per day, for one month and of an optional dose of the drug for another month and the gradual transition to dilantin sodium. The best results were obtained with dilantin, as shown by the number of patients who were entirely free of seizures and by a decrease in the average number of seizures per patient per month. A transitory increment was noted in some cases on transition from phenobarbital to dilantin. The complications encountered were hyperplasia of the gums, psychogenic phenomena and neurologic manifestations. FORSTER, New Haven, Conn.

THERAPEUTIC METHODS IN NEUROSYPHILIS. C. L. CARLISLE and U. S. BOWEN, M. Bull. Vet. Admin. **17**:125 (Oct.) 1940. SOBISMINOL MASS IN THE TREATMENT OF SYPHILIS. E. A. MCCLINTOCK, ibid. **17**:129 (Oct.) 1940. OPTIC NERVE DAMAGE IN LUETIC PATIENTS, C. E. JOHNSON, ibid. **17**:133 (Oct.) 1940.

The efficacy of chemotherapy, particularly with sobisminol mass, developed by Hanzlik, following hyperpyrexia for the treatment of neurosyphilis is discussed by Carlisle and Bowen, by McClintock and by Johnson. Carlisle and Bowen point out that hyperpyrexia induced by malaria or short wave diathermy should be complemented by chemotherapy, as it is likely that pyrexial therapy, with temperatures ranging from 104 to 107.6 F., will uniformly and for long enough heat all the tissues of the body to this spirocheticidal point. Therefore they believe that chemotherapy should take care of any spirochetes which escaped the spirocheticidal effects of the heat. For this McClintock believes that oral administration of sobisminol mass is indicated, as the daily urinary bismuth excretion level of from 3 to 5 mg. necessary for effective spirochetal destruction is easily maintained by its continued administration. This has been shown by various investigators. This level of excretion was easily maintained for the 4 patients treated at the Veterans Administration Facility at Palo Alto, Calif., by the daily oral administration of 900 mg. of sobisminol mass for as long as eight weeks. Mild toxic symptoms, such as nausea, vomiting, grip, stomatitis, anorexia and a bismuth line, do occur but did not in their patients. However, the toxicity is immediately relieved when the drug is discontinued. Because of toxic symptoms treatment with sobisminol mass had to be discontinued permanently with 4 and temporarily with 7 of 90 patients treated by Scholtz, McEachern and Wood. Johnson discusses the incidence of damage to the optic nerves and toxic amblyopia as by-effects of tryparsamide treatment of patients with neurosyphilis. He recommends routine ophthalmologic examination of the neurosyphilitic patient on admission to the hospital, as these findings will make subsequent comparisons possible. It has been stated by Moore that if any visual impairment is to occur it will appear by or before the fifth weekly injection of tryparsamide. If no impairment is apparent by the twelfth injection the drug may thereafter be administered with impunity. All patients should be cautioned to report any visual disturbance following tryparsamide therapy. Regardless of how psychotic the patient may be, any report of a visual change should be heeded and acted on immediately. At this time probably no changes will be apparent in the disk head provided treatment (hyperpyrexia and chemotherapy) for the neurosyphilis was instituted fairly early. Field changes must now be relied on; if present and tryparsamide is discontinued, it is usually possible to arrest the optic process. J. A. M. A.

VITAMIN B_1 IN TREATMENT OF POLIOMYELITIS. A. GISMONDI, Pediatria **48**:48 (Jan.) 1940.

Gismondi reports satisfactory results from the administration of vitamin B_1 in 13 cases of acute anterior poliomyelitis. The majority of the patients entered the hospital after establishment of the paralysis. The group included patients with acute, subacute and diffuse forms and patients with complete paraplegia or threatening ascending respiratory paralysis. The treatment consisted of intramuscular injections of 1 cc. each of a solution which contained 0.0025 Gm. of thiamine hydro-

chloride for each cubic centimeter of the solution (1,000 international units). The injections were given daily until from twenty to thirty-four had been administered. In 2 cases of diffuse poliomyelitis the injections were given twice a day for two weeks and once a day for another two weeks. In all cases the treatment induced rapid improvement of the paralysis and of the general condition of the patient. The disease was completely controlled in from three to four weeks. The patients recovered without sequelae, except in a few cases in which moderate sequelae were present.

J. A. M. A.

ACETARSONE IN DEMENTIA PARALYTICA. N. G. BLAIOTTA, Semana méd. **2**:266 (Aug. 1) 1940.

Blaiotta reports on a series of 15 unselected patients with dementia paralytica treated by subcutaneous injections of acetarsone and a bismuth compound. The injection, in a dose of 1 Gm. of acetarsone, was given three times a week in a series of twenty-one injections, with intervals of a month and a month and a half, respectively, between the first three series and of two months between further series. Duration of the treatment was determined by the behavior of the cerebrospinal fluid. The latter showed favorable alteration by the end of the first or second series when the results of the treatment were satisfactory, except when paradoxic reactions took place. The bismuth preparation was administered in combination with the arsenical treatment as soon as favorable modification of the cerebrospinal fluid was noted. Twelve of the patients were given the arsenical and bismuth treatment alone; 2 patients were given the treatment one year after failure of malarial therapy and insufficient arsphenamine treatment, and for 1 patient, in an advanced stage of the disease, the treatment was changed to malarial therapy, which failed. The dementia forms with agitation or with megalomania were predominant in the group. Only 1 patient was ambulant. The remaining 14 were kept in bed early in the course of the treatment. Of the group of patients treated with arsenic and the bismuth compound, 6 had a complete remission, 5 resumed work and 2 discontinued treatment in the course of incomplete remissions. One patient exhibited a paradoxic reaction of the cerebrospinal fluid with cyclic delirium. Two patients had physical and serologic improvement, but the mental condition remained unchanged. One died of cachexia in the course of the treatment, and the treatment of 1 failed. The 2 patients who had had malarial therapy improved. Twelve patients improved with the treatment, 2 died of dementia paralytica and the treatment of 1 failed. No complications occurred. The author concludes that the arsenical-bismuth therapy of dementia paralytica is effective and that blindness will not occur if proper indications and small doses evenly divided are adhered to.

J. A. M. A.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

SAMUEL BROCK, M.D., *Chairman of the Section, Presiding*

Joint Meeting, Nov. 12, 1940

Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E. DR. ISRAEL S. WECHSLER.

Last March (Recovery in Two Cases of Amyotrophic Lateral Sclerosis Treated with Tocopherol [Vitamin E], ARCH. NEUROL. & PSYCHIAT. **44**:470 [Aug.] 1940) I presented 2 patients with amyotrophic lateral sclerosis who had been treated with synthetic vitamin E (tocopherol), 1 of whom I wish to show again at this time. The diagnosis was questioned in the case of the other patient, but I am convinced that he has the disease; as proof I can report that his condition gets worse when he does not take the synthetic vitamin E and improves when he does. It will be recalled that the first patient, the woman, was in the hospital for several weeks; she was unable to get out of bed. She had marked atrophy of the tongue, fibrillations, increased reflexes and all the classic signs of amyotrophic lateral sclerosis. She had been practically paralyzed and had difficulty in chewing and swallowing. She was improved after treatment at that time. She is still able to walk, nine months later, although she is a little worse. There is some atrophy of the tongue. She eats well and has no trouble in swallowing.

The next patient to be presented now is a girl of 16, one of the youngest persons with this disease whose case is on record. Her condition dates back about a year. It began with weakness of the hand and difficulty in walking. On examination she showed the classic signs of amyotrophic lateral sclerosis. Although the girl was so young the classic triad, atrophy, fibrillation with increased reflexes and signs referable to the pyramidal tracts, left no room for doubt. When first seen she could not raise a pitcher—she had difficulty in performing any movement with her hand—and she had much more spasticity in her gait than she shows now. After treatment she could raise a pitcher with water in it. She improved so much that she was sent home after a stay of a few weeks in the hospital.

The third patient, aged 40, came last year with a classic case of amyotrophic lateral sclerosis. Her condition was far advanced; I sent her to the hospital. She had, in addition to the spastic gait, fibrillations, generalized hyperreflexia and atrophy. After a stay of several weeks she improved considerably; her gait improved; her strength increased, and she was able to go home and do some housework. She continued in this state for a while, and then grew worse. I increased her dose of vitamin E, and she again improved. Recently she has not had adequate treatment. Her tongue shows no fibrillations now, and only one or two indentations. There is little atrophy.

The next patient is a man of 41 whom I saw early this summer. He too had the typical form of amyotrophic lateral sclerosis. He gradually became worse under general treatment, to the extent that he could no longer walk, even with assistance. He could not rise from a chair; he needed at least two persons to help him stand at all. He was admitted to the hospital and was given massive doses of synthetic vitamin E. On admission his arms hung limply by his sides; he could not raise them at all. He has been in the hospital for four weeks. Under treatment with massive doses of the vitamin he can get up without help and walk.

The next patient is a man of 40 whose illness began in March 1940. He became emotional and cried and laughed without adequate reason. He had some difficulty in speaking and swallowing; all his symptoms were of bulbar type. On examination he had generalized fibrillations, mostly in the right shoulder, and generalized hyperreflexia. His voice is now about the same as when he left the hospital, but his arms are getting weaker.

The next patient is a young law student whose illness began presumably in January 1940 with weakness of the right hand. After he had been writing for three or four minutes the pen would drop and he could not go on with his work. He had fibrillations of the forearm, increased deep reflexes and atrophy of the hypothenar eminence. He had weakness of the adductor, flexor and extensor muscles of the fingers. After six weeks of treatment his strength recovered sufficiently so that he could take several four hour written examinations with the hand which previously could not write for more than five minutes. He has held his own since.

The next patient is a man of 59, a hospital worker. He had atrophy of the hands and generalized weakness, more marked in the upper extremities; he was unable to walk on the heels or the toes; he had generalized hyperreflexia and some fibrillations. When he was admitted to the hospital and given vitamin E he improved rapidly to the extent that he could, and can now, walk on his toes and heels. He is now back at his work. This man, too, when he could not get his medication grew weaker.

In addition to the 7 patients presented here, I could show perhaps 4 or 5 others who exhibited varying degrees of improvement, but I can cite at least 25 patients who have not improved at all with treatment. In fact, they have become worse while under treatment, but I am not concerned at this time with patients who have not recovered. Here are a few patients who after the administration of vitamin E showed improvement in varying degrees. In some the improvement was maintained. In others, in several in fact, the improvement reached a plateau, after which there was a dead line. Four patients had a specific history of food deficiency. Joe, the Italian patient, ate practically nothing but meat. For some reason, he ate no cereals, no bread, no spaghetti; he just lived on steak. I have several other patients who gave a specific history of dietary deficiency. One patient whom I did not bring here also showed improvement following aggravation of symptoms, and he, too, gives a history of vitamin E deficiency. One patient had dysentery and 2 others disease of the gallbladder, and all had antecedent deficiencies.

Without going into details, I may say with assurance that there are several kinds of amyotrophic lateral sclerosis, at least three, and possibly four. Only one of these will respond to vitamin E treatment. I should say it represents not more than a third, or perhaps a fourth, of the cases of what is called amyotrophic lateral sclerosis. It would seem that the whole chapter on amyotrophic lateral sclerosis, more particularly the form with the classic symptomatology, will have to be rewritten.

Experience accumulated thus far indicates that absence of vitamin E is not *the* cause, or the only cause, of amyotrophic lateral sclerosis, but is *a* cause in a certain number of cases. Some patients do respond to the administration of vitamin E; the majority do not. There are apparently several other factors which operate in this disease. Metabolic experiments on monkeys which my associates and I have carried on have resulted in death in 3 instances. There is some evidence that the nervous system has suffered. These investigations will be reported on later. Vitamin E, unlike some of the other vitamins, is so prevalent in nature that one should not expect dietary deficiency.

It has become evident that the therapeutic doses which have been given are much too low. Some patients have received daily as high as 1,000 mg. of tocopherol intramuscularly and the same dose by mouth without any ill effect. Some of the patients who did not do well on 100 mg. began to do well on 150 to 300 mg. given intramuscularly and 200 mg. or more by mouth.

I have made several other observations, one with regard to sex. It seems that females improve more than males. There have been no fatalities among the females, but there have been several among males.

DISCUSSION

DR. PETER G. DENKER: My interest in this work at Bellevue Hospital was aroused because of a personal relation with the patient in Dr. Wechsler's original case. Though the diagnosis was doubtful, I felt enthusiastic about the improvement of that patient and the manner in which it has been maintained. My associates and I were therefore in sympathy with this treatment, and we were not psychologically conditioned against it. In our neurologic service, Dr. Scheinman and I have been collecting a series of cases and have to date treated 14 patients with amyotrophic lateral sclerosis. We have been giving them between 100 and 200 mg. of alpha tocopherol daily, both orally and by hypodermic injection, for at least one month, but usually three months or even longer. Lately we have been adding vitamin B_6 in doses of 100 mg. daily. Unfortunately, we can report no success with any of the treatments. Three of the patients continued to grow worse and have died. Four or 5 have progressively become worse despite the therapy, and the condition of the rest has remained more or less stationary. As Dr. Wechsler has also found, we obtained in some cases temporary subjective improvement, which persisted for a varying period, usually a few weeks, and then the course has again been downhill. We felt much of this apparent improvement was due to the fact that the patients had been hospitalized and relieved of much effort and responsibility and were given more rest. One woman in particular, whose disease was in an early stage, despite large doses of vitamin E, became steadily worse so that, although at the start of treatment she was able to walk about the ward, after three or four months she was completely bedridden.

Though Dr. Wechsler feels there may be three or four types of amyotrophic lateral sclerosis, apart from the rare encephalitic or syphilitic picture resembling this illness, I am not sure whether this variation in the clinical picture is not all a matter of the rapidity of the course of the disease. In other words, I feel that the previous concept that all patients with this illness die within two or three years should be revised. We have a patient in our wards at present who has been ill for eight years, and we have many whose illness has persisted for longer than two or three years, although it is true that in the majority of cases the outcome is fatal within this time. It may be, therefore, that Dr. Wechsler's favorable results have occurred in those cases in which the course has naturally not been as rapid as it is in the majority—in other words, in those cases in which a plateau has been reached at which the illness will remain stationary for a varying period before another downward step in the progress occurs. It is important, therefore, that Dr. Wechsler see again these patients who have responded favorably at the end of another six months, before any final opinion as to the efficacy of this treatment can be expressed. In this respect it is interesting to note that at present Dr. Wechsler states he has attained favorable results in only approximately 25 per cent of the cases, whereas in his earlier reports he thought that the percentage of success was greater. This likewise would suggest that the illness may be running its customary course and that with the passage of time the results will not be as favorable.

As to the dietary deficiencies: At Bellevue Hospital, though we have inquired into the dietary habits of all our patients, we were not successful in eliciting a history of deficiency. In fact, one man was a vegetarian, who ate nothing but cereals, vegetables, salads, fruit juices, and the like; despite that fact, classic amyotrophic lateral sclerosis developed. We have also found it difficult to understand why, if this illness is due to vitamin E deficiency, more cases do not occur in the southern states, where so much pellagra and other ailments due to vitamin deficiency are encountered. I am not aware that the incidence of this illness in the South is any greater than in other parts of the country.

Furthermore, it is interesting to note that in experimental work on animals in which vitamin E deficiency is produced, one frequently gets encephalomalacia,

which is not encountered in the clinical picture seen in man. A patient with amyotrophic lateral sclerosis is almost always clear mentally until the end, and this should likewise lead one to believe that a vitamin E deficiency may not be the sole factor.

I regret that our results lead us to differ with Dr. Wechsler; he has rendered a valuable service in stimulating interest in an illness which has always been looked on as hopeless.

DR. CHARLES DAVISON: Twelve patients were treated with vitamin E at the Montefiore Hospital. Oral administration of 15 mg. daily plus intramuscular therapy was carried out for an average of two to four months.

For one month, because of inability to get the material, these patients received no treatment. Then 50 mg. was given daily by mouth, with no intramuscular injections. All the patients had rather advanced amyotrophic lateral sclerosis. Most of them had bulbar symptoms, and all were past the age of 40. A few of these patients had received vitamin E treatment before entering the Montefiore Hospital, 1 at Mount Sinai Hospital and 1 elsewhere.

The condition of 1 patient was diagnosed by some as amyotrophic lateral sclerosis and by others, including Dr. Wechsler, as progressive muscular atrophy. After treatment he was able to adduct his arm 30 degrees or more. Another patient noticed temporary subjective improvement in swallowing and in movements of the hand. One patient receiving tocopherol noticed no change. After the treatment was stopped, he claimed that the fibrillations were not as marked.

Objective improvement was noted only in the first case. All the patients who received treatment have become slowly but steadily worse. Five of the 12 patients died—4 of respiratory failure and 1 of pneumonia.

In correlating the results at Montefiore Hospital with those reported by Dr. Wechsler, there is some valid criticism to be offered of the cases I report. The disease was in a far advanced stage; the patients did not receive adequate treatment, and perhaps many of them did not fall into the group of persons with amytrophic lateral sclerosis who respond to vitamin E. Whatever the results may be, Dr. Wechsler has rendered a valuable service in the reinvestigation of amyotrophic lateral sclerosis. In the near future one will undoubtedly have a better understanding of this disorder and its various etiologic agents.

DR. RICHARD BRICKNER: I wish to call attention to two manifestations of the effect of the treatment in Dr. Wechsler's patients. The first concerns the obese patient. Five weeks or so ago, when he came into the hospital, he could not stand without the support of two people. Since, he has become able not only to stand but to walk alone. Despite his obesity, which is unusual in a patient with amyotrophic lateral sclerosis, he unquestionably has the disease. By now he walks all over the ward by himself. The change in him seems to me impressive.

The other case is that of the woman in the wheel chair. Perhaps the most measurable improvement is in her tongue. On her admission to the hospital, in August 1939, her tongue showed the "bag of worms" phenomenon so well that she had what might be called a "teaching tongue." Now there is not a fibrillation to be seen in it.

Dr. Wechsler did not have time to discuss what relation there may be between vitamin E deficiency and other coexisting deficiencies. Vitamin E deficiency, in particular, should not be present alone, without a similar deficit in other factors. I remember, for example, that I saw the woman with the "bag of worms" tongue a few weeks before the vitamin E treatment was started. I gave her thiamine hydrochloride, and there was moderate but indisputable improvement in the tongue under that regimen.

I wonder whether in other cases, both those in which vitamin E is effective therapeutically and those in which it is not, similar adjunctive measures may not also be important. Dr. Wechsler has stated that the patients do better in the hospital than at home. May it not be that some other factor in hospital life is important, such as rest, improvement in the general food intake and the presence

of a nurse to insist on the patient's eating? Such influences as these may support the vitamin E treatment, or perhaps be of more general significance than the therapy alone.

Still another adjunctive factor is indicated by the fact that the patients who have responded best are menstruating women, a point which has brought the use of endocrine substances into the field.

In summary, I have the impression that Dr. Wechsler's presentation of these patients offers not only grounds for hope but an approach which may lead to greater understanding of the disease.

DR. THEODORE R. ROBIE, East Orange, N. J.: I wish to mention 1 case, that of a boy aged 11, unfortunately not a case of amyotrophic lateral sclerosis but one of interest in that treatment with vitamin E was employed. The illness was diagnosed as pseudohypertrophic muscular dystrophy. This boy has shown marked improvement under continued treatment with vitamin E and vitamin B_1. He could not go up or down stairs before he began vitamin E therapy; now he goes upstairs alone without crutches and without help. He comes downstairs in a lively manner. It remains to be seen whether the improvement will continue, but it has been maintained for two months.

MEMBER OF AUDIENCE: May I ask Dr. Wechsler whether examinations of the semen have been made on any of the male patients? Did any of the patients, male or female, show any indication of lack of bile secretion, anything which would interfere with the absorption of fat? Some work has been done on animals indicating that vitamins A, D and E all require bile and bile salts for their absorption.

DR. ISRAEL WECHSLER: Unfortunately, because of limitation of time, I left out a great many things. Some patients were given estrogen, and 1 showed definite improvement after its administration, an improvement which she did not show with vitamin E alone. There is some experimental evidence in rats which points to sex differences in response. When the rats are deprived of vitamins, the female will have smaller litters, fail to become pregnant or abort. If vitamin E is administered in time the process can be reversed. If, however, testicular atrophy occurs in the male, administration of vitamin E will not reverse the process. There may be, then, a difference in some response in the male as compared with that in the female. The semen was not examined, but I should add that the *facultas coeundi* in the male is not impaired.

The question of the administration of bile has been raised. Reasoning by analogy with vitamin K, which also is fat soluble and is better absorbed if bile is given, we administered bile salts to some of our patients. Here, again, we cannot properly evaluate results. Some patients said they felt better; to most it made no difference.

This raises again the whole problem of absorption, which seems to me extremely important. To repeat, there seems no reason that there should be any deficiency of vitamin E in human beings. I stated that 4 or 5 patients had deficiencies because they did not eat foods containing the vitamin, but the vast majority had adequate diets. The conclusion, therefore, is justified that absorption and utilization are faulty.

What Dr. Brickner said is important, and I agree with him. Two statements may be made about vitamins, which apparently are contradictory but in reality are not. First, most vitamins act specifically, and their privation or administration brings about specific results. This seems to be true biologically of vitamin A, the various forms of vitamin B and vitamins C and D. It is possible, though I do not know, that vitamin E also acts specifically. If this is true, the indiscriminate administration of "shotgun" prescriptions of vitamins is not a scientific procedure. On the other hand, there is ample evidence to show that rarely is there a deficiency of one vitamin alone: Clinically one observes multiple deficiencies. The various vitamins may act synergically with one another. It remains to discover those synergisms. I should add that studies on this phase are being carried on. So far,

chemical determinations on the blood and functional studies of the gastrointestinal tract and liver have failed to give significant results. My collaborators and I may be able to report on some chemical studies in the near future.

Finally, permit me to repeat that, realizing how treacherous therapeutic claims can be, I am making none. I know that in a certain proportion of cases, possibly 20 to 30 per cent, one observes varying degrees of improvement when synthetic vitamin E is given, and the conclusion may be drawn that there is a deficiency of this vitamin in amyotrophic lateral sclerosis. But it is clear that there must be a number of x factors in addition. What they are is not yet known. If there is even slight or temporary improvement the fact is of extreme importance. It may be true, as Dr. Denker says, that the recovery is not permanent and that there are relapses, but one thing is certain, I have never before seen, nor has any other neurologist, the slightest improvement or remission in cases of amyotrophic lateral sclerosis. Temporary arrest of progress may have occurred spontaneously, but never before actual remission, however temporary, or improvement, however slight. Time alone will tell whether the remissions of three and six months and the varying degrees of improvement will have the significance which I believe they possess.

Changes in Cerebral Blood Flow and Arteriovenous Oxygen Difference During Insulin Hypoglycemia. Dr. Harold E. Himwich, Albany, N. Y. (by invitation); Dr. Karl M. Bowman; Dr. Cornelius Daly (by invitation); Dr. Joseph F. Fazekas (by invitation); Dr. Joseph Wortis (by invitation), and Dr. Walter Goldfarb (by invitation).

Because it was suggested that the smaller arteriovenous oxygen difference observed during insulin hypoglycemia may have been caused by more rapid flow of blood through the brain and not by diminished cerebral metabolism, and because such an interpretation would alter fundamentally the present concepts of cerebral metabolism, it became necessary to determine simultaneously the cerebral blood flow and the arteriovenous oxygen difference. The changes in blood flow during insulin hypoglycemia, uncomplicated by convulsions, were not of great magnitude and usually exhibited a slight diminution. Thus, the decrease in the arteriovenous oxygen difference during insulin hypoglycemia could only have been caused by impaired cerebral metabolism, and the slower blood flow showed that the decrease in metabolism was even more profound than could be expected from the smaller arteriovenous oxygen difference. The injection of dextrose increased the arteriovenous oxygen difference and as a rule had but slight effect on the cerebral blood flow. This increase in cerebral metabolism was reflected in the altered clinical condition of the patients, who awakened from coma and regained contact with the environment. The administration of lactic and pyruvic acids likewise had no significant effect on cerebral blood flow. However, the cerebral arteriovenous oxygen difference did not increase sufficiently to awaken the patient from coma. It is difficult to understand why lactic and pyruvic acids, which in vivo support cerebral metabolism as well as dextrose, do not significantly increase cerebral metabolism in vivo. It is suggested that lactic and pyruvic acids are oxydized at a slow rate, a rate which stimulates the diminished cerebral metabolism characteristic of excised tissues but is not sufficiently rapid to support the high requirements of the brain in situ. Though the oxidative process which includes the formation of lactic and pyruvic acids is not important quantitatively with regard to the amount of energy produced for the brain in situ, it is an obligatory preliminary step affording the energy for the phosphorylation of dextrose. In beriberi, pyruvic acid is not oxidized and therefore phosphorylation of dextrose cannot take place. In hypoglycemia, dextrose is not available either for phosphorylation or for the formation of pyruvic acid.

DISCUSSION

Dr. Tracy J. Putnam: This investigation forms an interesting complement of work which was done on animals by Maddock, Hawkins and Holmes, which I

had the pleasure of watching (Inadequacy of Substances of "Glucose Cycle" for Maintenance of Normal Cortical Potentials During Hypoglycemia Produced by Hepatectomy with Abdominal Evisceration, *Am. J. Physiol.* **125**:551-565 [March] 1939). These workers produced hypoglycemia in rabbits by hepatectomy and evisceration, which prevented the reformation of glycogen from lactic and pyruvic acids and other dextrose fractions. They watched the effect on the electroencephalogram as the blood sugar decreased. They found, as did Dr. Himwich and his collaborators, that any of the breakdown products of dextrose utilized in the metabolism of muscle, such as pyruvic acid, fumaric acid or lactic acid, were inadequate to maintain a normal electroencephalographic record. It seems to me, therefore, that one must conclude that the brain has the most rigid energy requirements of all tissues of the body. One must recognize that the methods used by Dr. Himwich and his collaborators are greatly superior in many ways to studies in vitro, in which the conditions are far from physiologic. I should like to ask Dr. Himwich whether he thinks it is possible that the oxidation of dextrose goes no further than lactic acid, which then escapes into the blood, so that one does not need to suppose it is further broken down, even at a slow rate. It seems to me that if there exist a cycle in which large amounts of dextrose are used up and made into lactic acid and a slower cycle in which a little lactic acid is burned up it would be inevitable that the lactic acid would accumulate or be forced out into the circulating blood. I think there is some evidence that it is forced out into the circulating blood or surrounding tissues, namely, that under conditions of oxygen deficiency the p_H of the brain swings rather rapidly upward.

The relation of this work to diseases of the nervous system is not wholly clear, but is certainly important. One should think of it, first, in relation to diseases in which the function of the brain is inefficient—the mental deficiencies and psychoses. One must think of it also in relation to convulsions, for there is much reason for believing that in the course of a convulsion the type of metabolism in the brain cells is abnormal. Just how it is abnormal I hope Dr. Himwich and his collaborators will tell at a future meeting.

Dr. Ephraim Shorr (by invitation): I welcome this opportunity to discuss the work of Dr. Himwich and his collaborators, having followed with interest his studies in cerebral metabolism for many years. His demonstration that no matter what the metabolic situation in the organism, the brain oxidized nothing but carbohydrate and that, in contrast to the other tissues in the body, it did so independently of insulin, was a milestone in the understanding of metabolism of the brain. There is no other example of complete independence of insulin on the part of tissues, although there is partial independence in the mammalian heart, which can store glycogen in the absence of insulin but cannot oxidize it. Dr. Himwich's demonstration of the complete dependence of the brain on carbohydrate as a substrate led logically to his studies of cerebral metabolism during insulin hypoglycemia. He was able to show that when the true sugar content of the blood is reduced by insulin to virtually zero no other foodstuffs can serve as fuel for the brain and the respiration of the brain is sharply reduced, as evidenced by the striking decrease in the arteriovenous oxygen difference in the blood passing through this organ. The brain itself has such small stores of carbohydrate that it is uniquely dependent on a constant supply from the blood stream. When this fails the oxidation level is reduced so greatly that consciousness is not maintained.

It was necessary, however, to examine the possibility that the markedly accelerated blood flow might explain the low arteriovenous oxygen differences, since increased blood flow during insulin hypoglycemia had been observed in other structures. That such is not the case and that the inferences of Dr. Himwich and his collaborators were correct became apparent this evening.

From here the picture is not quite as clear, although I think that Dr. Himwich's conclusion that there are several pathways of carbohydrate oxidation in the brain is probably correct. I should like to raise a few points with which he and his co-workers might deal subsequently, as they have so well dealt with the suggestions made as to their previous work. It has been assumed all along that the

metabolic process observed in vitro with normal brain, namely, an oxidation of dextrose through intermediary stages of lactic and pyruvic acids, may be the normal channels for carbohydrate oxidation. Under artificial conditions induced by nicotine, studied by Himwich, and by iodoacetic acid, studied by my associates and myself, dextrose can be oxidized by the brain without going through the lactic acid–pyruvic acid stages.

Dr. Himwich now brings up the possibility that these shunts, which up to now have been regarded as pathologic, may quantitatively be the most important in the living organism. The basis for this inference is the failure of injections of lactic and pyruvic acids to stimulate the metabolism of the brain.

This reasoning is dependent on the unusual sensitivity of brain to very small amounts of dextrose. We have shown with washed brain in vitro that with about 15 to 20 mg. of dextrose per hundred cubic centimeters the rate of oxidation is virtually maximal. Whether or not the same sensitivity exists for lactic or pyruvic acids is not known. It may well be that the concentration of the latter substrates must be higher in the medium or in the circulating blood before oxidation is stimulated and that the actual concentration of these substances in the cell is different from that in the circulating body of fluids. On these assumptions it is conceivable that the values for lactic and pyruvic acids produced in the blood stream by the amounts which Dr. Himwich injected were too low. The lactic acid used was the racemic form, consisting of equal parts of lactic acid utilizable by the organism and lactic acid of the non-natural, unutilizable type. The elevation of the lactic acid of the blood to 40 mg. per hundred cubic centimeters would therefore not represent a true lactic acid level, since one half of this could not be utilized by the organism. So also with pyruvic acid, the levels reached after injection of less than 3 mg. per hundred cubic centimeters is extremely low. To make this point completely clear, it would be necessary to attain much higher levels of both lactic acid and pyruvic acid in the blood stream. I hope that presently Dr. Himwich and his co-workers will be able to give the results of their experiments carried out under these more conclusive conditions.

MEMBER OF AUDIENCE: I should like to mention some work on heat production of the brain in vivo in animals during insulin hypoglycemia. The administration of dextrose produced stimulation of the brain and an increase in heat production. As heat production is an indicator of the metabolism of the brain, this observation is in agreement with the findings of Dr. Himwich and his co-workers.

DR. JOSEPH WORTIS: I should like to remind those present that just as clinical shock has been pushed into the foreground in describing insulin treatment, so, too, in consideration of the physiologic basis of these treatments the temporary diminution in cerebral metabolism has occupied most of the attention. It is perhaps well to remind oneself that, in addition to the changes reported in the authors' presentation, literally dozens of other changes have already been reported in the literature, with respect both to chemical changes in the organism as a whole and to physiologic alterations in the brain itself. I mention at random changes in serum lipids, electrolytes, water metabolism, peripheral blood flow, chlorides and cortical p_H, any or all of which may be significant in the determination of the therapeutic mechanism of the shock treatment. In addition to those we have presented tonight, other significant physiologic changes in the brain have been reported: At Bellevue Hospital, for example, we have lately had occasion to report changes in the arterial carbon dioxide content in cases of insulin hypoglycemia. In practically all of the cases we studied there was a sharp and consistent increase in the carbon dioxide content of the arterial blood, with a particularly sharp rise to as much as 10 volumes per cent above the normal level before a convulsion. This affords a striking confirmation of the findings of Gibbs, Lennox and Gibbs (Variations in the Carbon Dioxide Content of the Blood in Epilepsy, ARCH. NEUROL. & PSYCHIAT. **43**:223-239 [Feb.] 1940). Perhaps in time all these diverse findings will fit into a single composite picture which will throw light on the significant therapeutic mechanism of the treatment.

MEMBER OF AUDIENCE: I should like to ask Dr. Himwich if he has any explanation for the fact that the arteriovenous oxygen difference does not return to normal, even though the blood sugar has returned to the previous level after administration of dextrose.

DR. HAROLD E. HIMWICH, Albany, N. Y.: Dr. Putnam asked about the breakdown of dextrose to lactic acid. It is known that the brain has this ability to a high degree, and yet it is difficult to disclose the importance of lactic acid by examination of cerebral blood. Under ordinary conditions there is no apparent difference between the lactic acid content of the blood entering and that leaving the brain. It may be, as Dr. Shorr mentioned, that if lactic acid reaches a sufficiently high concentration it may be utilized as readily as dextrose. The present observations reveal that pyruvic and lactic acids are not utilized rapidly by the brain in vivo. Quantitatively they are not an important supply of energy. However, the recent work of Cori suggests a special role for pyruvic acid in the metabolism of the brain.

I was glad to learn of the experiments in heat production during hypoglycemia. Heat production, like oxygen uptake, measures energy exchange. These experiments give additional evidence for the conception that cerebral metabolism is largely dependent on carbohydrate.

Dr. Wortis emphasized that many changes occur during insulin hypoglycemia. I should like to remind the audience that none of these other changes occur until hypoglycemia develops. Which of the many changes is the most important in the alleviation of schizophrenia we cannot say.

Finally, in regard to the last question, namely, the incomplete restoration of the arteriovenous oxygen difference, it should be noted that these values are associated with the time when the patient first makes contact with the environment. Other samples of blood drawn a little later might reveal higher values. It requires some time before all parts of the brain return to full function after hypoglycemia.

LEON H. CORNWALL, M.D., *President of the New York Neurological Society, Presiding*

Joint Meeting, Jan. 7, 1941

Neuropsychiatric Disturbances in Addison's Disease and Role of Impaired Carbohydrate Metabolism in Production of Abnormal Cerebral Function. DR. GEORGE L. ENGEL (by invitation) and DR. SYDNEY G. MARGOLIN (by invitation).

Although Addison's disease is uncommon, it offers an ideal preparation for the study of the role of deranged metabolism of the central nervous system in the production of neuropsychiatric symptoms associated with many conditions. On the one hand, this is due to the almost exclusive dependence of the brain on carbohydrate as the chief substrate for normal metabolism, and, on the other, to the presence of adrenal insufficiency, which involves a disturbance of the normal salt and water balance and of carbohydrate metabolism. Of the latter, the more important in cerebral function, the following features are most significant: (1) slightly impaired absorption of dextrose from the gastrointestinal tract; (2) decreased ability to form new dextrose from the intermediary products of carbohydrate and protein metabolism; (3) corresponding increase in the utilization of exogenous carbohydrate at the expense of fat and protein; (4) rapid exhaustion of available carbohydrate stores, including liver glycogen; (5) markedly increased sensitivity to factors which normally lower the blood sugar level, such as insulin with failure of normal homeostatic mechanisms to counteract the resultant hypo-

glycemia, and (6) a low fasting blood sugar level and flat sugar tolerance curve, with terminal hypoglycemia.

With this type of metabolic disturbance, it is seen that patients with Addison's disease not only may have an insufficient supply of carbohydrate available for normal requirements of the brain but also may be unable to utilize efficiently what is available. Thus it is possible to have symptoms of carbohydrate deprivation at relatively normal blood sugar levels. With these facts in mind, it is not surprising that a review of the literature reveals that practically every type of neurologic and psychiatric manifestation may occur in Addison's disease.

A case is described of a man aged 26 with proved Addison's disease of six years' duration who, during a six months' period in which he received no replacement therapy, manifested marked changes in personality, deterioration of habits, periods of amnesia and unreality, a dyskinetic syndrome, including choreoathetosis and hemiballismus, trismic speech and, finally, convulsions. He was found to have a marked disturbance of carbohydrate metabolism, with a low fasting blood sugar level, a flat sugar tolerance curve, reaching hypoglycemic levels in three to four hours, a huge spontaneous appetite for carbohydrates (800 Gm. on a free diet), a normal basal metabolic rate, fairly rapid absorption of carbohydrate, as evidenced by prompt response of hypoglycemic reactions to oral administration of dextrose, and no glycosuria. His electroencephalogram showed diffuse, slow activity, with frequencies of from 2 to 6 per second and amplitudes as high as 75 microvolts, but no cortical focus. It was possible to control the patient's symptoms and to improve the electroencephalogram to a moderate degree by a continuous high carbohydrate diet (600 to 800 Gm.) and administration of desoxycorticosterone acetate. Much greater benefit resulted from the use of aqueous adrenal cortex extract, which also effected an improvement in the dextrose tolerance curve.

As confirmatory evidence of impaired gluconeogenesis, the fasting pyruvic acid content of the blood, determined by the method of Bueding and Wortis (*J. Biol. Chem.* **133**:585 [April] 1940), was found to be consistently elevated, ranging from 1.53 to 1.83 mg. per hundred cubic centimeters, and to be greatly increased after ingestion of dextrose. Since fasting pyruvic acid has been reported to be increased only in cases of thiamine deficiency and since independent data have shown that both the vitamin B complex and the sterols of the adrenal cortex are prominently concerned with similar phases of the intermediary metabolism of carbohydrate and protein, an attempt was made to achieve further improvement by the use of massive doses of nicotinic acid amide (300 mg.), thiamine hydrochloride (30 mg.) and riboflavin (15 mg.) daily. This resulted in an almost complete remission of neuropsychiatric symptoms; the electroencephalogram became of borderline normal type; the dextrose tolerance curve changed sharply in character, maintaining a high plateau level for three hours; spontaneous carbohydrate requirements were reduced to an average of 450 Gm. daily; the patient gained 22 pounds (10 Kg.) in a three month period of observation, and he was able to return to work and normal social activity. Further observation indicated that optimum control resulted from the combined use of aqueous adrenal cortex extract and the members of the vitamin B complex cited.

This case represents a carefully studied instance of profound neuropsychiatric disturbance produced by metabolic factors in which correction of some of those factors resulted in almost complete remission of symptoms. With the aid of the electroencephalogram and studies of carbohydrate metabolism, we have delineated a group of cases in which neuropsychiatric disturbances were present and there was evidence of impaired or inadequate carbohydrate utilization by the central nervous system. The cases represented such diverse conditions as Addison's disease, rheumatoid arthritis, ulcerative colitis, anorexia nervosa, periarteritis nodosa, Guillain-Barré syndrome, cirrhosis of the liver and avitaminosis, in all of which the nature of the disturbance in carbohydrate metabolism is by no means clear. It may depend on a variety of exogenous and endogenous factors, including hormone imbalances, nutritional defects, vitamin deficiencies, toxic conditions, perversions of appetite, deranged homeostasis and other disorders as yet poorly defined and

poorly understood. But all these cases have in common neuropsychiatric disturbances of widely varying character, with striking fluctuations from time to time. All are associated with deranged carbohydrate metabolism, as evidenced by flat dextrose tolerance curves, with a tendency toward very low values after four to five hours, and sometimes by marked appetite for carbohydrates. In all instances the fasting electroencephalogram revealed a striking cerebral dysrhythmia, brought out best by hyperventilation but also present on the spontaneous record in many instances, which could be completely abolished by administration of dextrose (Engel, G. L., and Margolin, S. G.: Clinical Correlation of the Electroencephalogram with Carbohydrate Metabolism, this issue, page 890). In all cases in which the primary condition had cleared clinically, the electroencephalogram and the dextrose tolerance curves likewise more closely approximated normal.

It is suggested that these cases illustrate a dynamic neuropsychiatric symptom complex, secondary to internal disease, in which there may be significant implications for active therapy along metabolic lines.

DISCUSSION

DR. ISRAEL WECHSLER: The authors forgot to state that the work was done in the neurologic service. I stress this because of the frequent accusation, sometimes not unjust, that the neurologist is interested only in diagnosis. The work illustrates the trend of neurology from static pathology and anatomy to physiology, chemistry, pharmacology, vitamin metabolism, electroencephalography and so on.

Increasing attention is being paid to minor neuropsychiatric symptoms of patients who are generally regarded as psychoneurotic. Such manifestations as minor behavior disturbances, fleeting syncopes and bizarre seizures have been studied from the point of view of hypoglycemia and its correlation with electroencephalographic patterns. The abnormal sugar curves, the abnormal rhythms on hyperventilation and the electroencephalographic disturbances on withholding or administering dextrose, on compression of the carotid sinus and on postural changes have helped not only in evaluating the convulsive state but in detecting unsuspected organic changes.

Of fundamental importance is the demonstration by the authors of the role played by vitamins in the hypoglycemia of Addison's disease. I do not know whether the pyruvate index is to be regarded as a guide. The normal figures may be higher than one suspects, and they are not altogether significant. Furthermore, after the administration of vitamins and dextrose and the disappearance of symptoms the pyruvates may still remain high. However, the fact that the patient reported on, who first had thromboangiitis obliterans and then manifested Addison's disease, could get on with vitamins alone, without desoxycorticosterone (and he has done well on this treatment for the past three months), is of signal importance.

The investigations briefly alluded to have led to the study of other patients with what appeared to be hysteria, simulation, minor seizures, subclinical avitaminoses, syncopes, carotid sinus sensitivity and dyskinesias. One patient had a Guillain-Barré syndrome and a hypoglycemic curve. All responded to more rational therapy than is vouchsafed by ordinary sedative medication.

DR. NORMAN JOLLIFFE: I shall confine my discussion to the pyruvic acid curves. First, the normal person has a low pyruvic acid content of the blood, that is, below 1.2 mg. per hundred cubic centimeters. Second, all patients with undoubted clinical evidence of thiamine deficiency who have so far been observed had increased amounts of pyruvic acid, that is, above 1.3 mg. per hundred cubic centimeters. Third, when stress or strain is thrown on the thiamine-deficient person, as when dextrose is given by mouth, it is found that the pyruvic acid is greatly increased and does not return to the fasting level within three hours. I should like to point out the difference between the cases of thiamine deficiency which my associates and I have studied and the cases reported by Drs. Engel and Margolin. In their case of Addison's disease the pyruvic acid level was abnormally high. When they gave the patient dextrose the amount of pyruvic acid in the blood increased over the fasting level, but it returned within three hours to the fasting level. In our patients the pyruvic acid increased, but it did not return to the fasting level within

three hours. Frankly, I am unable to explain this, unless there may be a different mechanism in the case of Addison's disease than that which is responsible for the same effect in cases of thiamine deficiency.

The Narcoleptic-Cataplectic Syndrome: An Excessive and Dissociated Reaction of the Sleep-Regulatory Mechanism, and Its Accompanying Mental States. DR. SAMUEL BROCK and (by invitation) DR. BENJAMIN WIESEL.

This paper will be published elsewhere.

Oliver Wendell Holmes: A Precursor of Freud. DR. C. P. OBERNDORF.

Oliver Wendell Holmes (1809-1894) lived and worked at a time when two opposing tendencies were developing in New England. One was represented by the advance of science; the other, by an indulgence in cults tinged with mysticism. Both tendencies were reactions against the rigid repression of New England life. Of course Holmes's interests fell with the scientific.

As a result of his rebellion against the ideas of predestination and preordination he formulated certain theories in which he denied the possibility of the complete freedom of the will on the basis of unconscious mentation. In 1871, in an essay entitled "Mechanism of Thought and Morals," read before the Phi Beta Kappa society and published in "Pages from an Old Volume of Life", he stated his concept of the nature and effects of unconscious mentation, which is very similar to that advanced by Freud twenty years later. Not only is the concept similar, but the principles and nature of dream life, the quality and manner of thought flow, the theory of thought association, the question of psychic dualism, the difference in the quality of thought in males and in females and the effects of sexual frustration are clearly and definitely stated.

Holmes undoubtedly came to these conclusions from observations at the bedside and in the consultation room. His three novels, "Elsie Venner," "The Guardian Angel" and "A Mortal Antipathy," all written late in life, are essentially clinical case studies of hysteria and neuroses. They reveal that Holmes was acquainted with the essence of that system of psychology later called psychoanalysis by Freud, and that he was an extremely competent psychiatrist in the modern definition of that specialty.

DISCUSSION

DR. TRACY J. PUTNAM: I have been given the honor of discussing Dr. Oberndorf's paper, presumably not as a surgeon but as one brought up in the ways of a Boston which has vanished and in the tradition of Oliver Wendell Holmes. It gives me a peculiar satisfaction to hear this testimony to Holmes's many-sided genius.

Holmes's outstanding characteristics were his openmindedness, his scholarship and his versatility. These qualities were well shown in his discussion of the contagiousness of puerperal fever, which was founded largely on his impression of the experiences of his colleagues and on an intensive study of the literature, rather than on controlled observations of his own. Semmelweiss, on the other hand, relied almost entirely on a study of personally observed cases and reported overwhelmingly convincing statistics. Semmelweiss was apparently unaware of Holmes's observations, which is not surprising, for even now American contributions to science are apt to be disregarded on the other side of the Atlantic. Holmes, for his part, gave prompt and due credit to Semmelweiss at a time when the latter was enduring a torrent of abuse in his native country.

Aside from his recognition of the nature of puerperal fever, Holmes was not a great originator. He invented a form of microscope stand for students, devised the type of stereoscope which is still in common use and made a few minor observations in anatomy and physiology. His claim on history rests largely on his ability to read, accept, grasp, systematize and expound scientific ideas and on

his important and wholly beneficent influence on the development of American literature. His was a civilizing genius, rather than a creative one.

It is, I believe, in this light that his description of the unconscious must be viewed. The article of which Dr. Oberndorf speaks and the one entitled "The Human Body and Its Management," which precedes it in "Pages from an Old Volume of Life," are both popular summaries, neither of which purports to embody any original data. Holmes attributed his conception of the unconscious to Leibnitz and acknowledged that the material he presented was borrowed from Hamilton and Mill, Abercrombie, Laycock, Maudsley, Herschel, Carpenter, Lecky, Dallas, Hartley, Huxley and others. It seems to me strange that Van Wyck Brooks should speak of Holmes as playing into the hands of Darwin, when the article in question shows that Holmes had not only read but easily accepted Darwin's work published a few years previously. In common with other poets and philosophers, he had an intuitive grasp of many psychologic facts, enriched by a sympathetic contact with his patients' problems (as may be inferred from his description of the doctor in "Elsie Venner"). An interesting forecast of the principle of repetition, for example, is found in the following stanza:

> "Minds roll in paths like planets; they resolve
> This in a larger, that a narrower ring
> But round they come at last to that same phase
> That selfsame light and shade they showed before."

But I find it difficult to believe that he was, or ever considered himself, a pioneer in medical psychology.

His breadth, grasp and ability to teach have surely not been wasted in medicine. Among his pupils were Henry Bowditch, William James and James Jackson Putnam; two of these three were also relatives and personal friends of his.

To turn from Holmes to Freud, I should venture to question whether Freud ever believed that the conception of the unconscious was his own. The term was in current use at the time his theories were forming, and he utilized it substantially in its accepted meaning, as has been pointed out with particular clarity by Levine, in his book entitled "The Unconscious." He did not stop with the conception, however. He went on to show that the content of the unconscious could be explored by a definite technic and that much of the material brought up from it had disappeared from consciousness because of a process of repression. Unlike any of his predecessors who had used the term, he accumulated an enormous volume of observations on the spontaneous productions of his own patients, systematized them, deduced certain principles from them and made a practical application of the principles. It is in this sense that Freud's work is dynamic, a term which can scarcely be applied to any of the other psychologic systems of his time.

Dr. John Alfred Parsons Millet (by invitation): I feel privileged to have heard this paper of Dr. Oberndorf's, after hearing an equally interesting paper on Nathaniel Hawthorne which he gave before the New York Psychoanalytic Society. It seems to me a matter of considerable interest that in the writings and thoughts of these two such different types of New Englanders one should find elements which suggest some of the dynamic principles expressed later in the work of Freud. It is interesting to hear what Dr. Putnam has said about the difference between the significance of such writing and such thoughts and the real contributions to human learning made by a mind such as that of Sigmund Freud. It is interesting to me, also, to compare the New Englander, with his long tradition of repression, with Sigmund Freud, a representative of an oppressed race in Europe, and to reflect on the possibility that there was a good deal of rather deep insight into the significance of the unconscious among the New Englanders long before it was brought to the surface by the remarkable researches of Freud. It is difficult to think of two more different types than Hawthorne and Holmes. Holmes seems to represent a certain type of Yankee with whom any one who

has been brought up or lived in the New England states has come to be familiar. The outstanding features of such personalities seem to be a vast friendliness and an extraordinary ability to observe life, and above all an amazing ingenuity in devising new contraptions. One of Freud's great virtues likewise is the remarkable ingenuity which he showed. Why should he have been able to turn this knowledge, which had been in the hands of many hundreds of people before him, into such an extraordinary channel of investigation? Certainly, the chief feature of that ability is the faculty which is called ingenuity. In that sense I think one can say that Holmes was really a precursor of Freud.

Also, it is interesting to reflect that James Putnam, when he came forward with his advocacy of Freud, was bitterly attacked by the Boston brahmins of medicine and of the laity with the same degree of intensity with which Freud was attacked in the scientific circles of Vienna. It is almost as though James Putnam might be looked on as a steppingstone between Holmes and Freud in that respect. Holmes did not take much stock in these observations on the unconscious which he made. He chose to make them in an address before the Phi Beta Kappa society, so I judge that he did not make them with the same seriousness that he would use in speaking on puerperal fever before the Boston Society for Medical Improvement. He was not aware of the significance of his own thinking; Putnam, on the contrary, was aware of the significance of his thinking, and it was for that reason that he became a martyr to his beliefs in much the same way that Freud did later. I do not believe that one can think properly of Holmes as a phenomenon in the same way that one can of Freud. There are a great many Yankees like Holmes, and many of them almost as active and almost as versatile, though not with the same brilliance of mind. With Freud there is no question but that he was, and always will be, a real phenomenon. The incidence of a human phenomenon in the course of history is something about which it is always tempting to speculate. Why should Freud have appeared at the turn of the century? It is perhaps amusing to think that his "Interpretation of Dreams" appeared within a very short time of the death of Queen Victoria.

DR. C. P. OBERNDORF: I should like to thank Dr. Putnam and Dr. Millet for their discussion. I think that Dr. Putnam has been correct in calling attention to the annotations which Holmes made to his essay, indicating that his formulations were the result not only of previous investigations, for the citations are numerous, but of his ability to combine these observations of others with his clinical experience. It is curious that all his novels were written late in life; "A Mortal Antipathy" is really a case report. In the prefaces to all of his novels Holmes explains that the topics approach a new field, one in which he is unlikely to be believed, one in which he is advancing an entirely new theory. Thus, in "A Mortal Antipathy" Holmes pictures a child who is allowed to fall from a young lady's arms and becomes unconscious. Subsequently, every time that an attractive girl appears the child goes into a convulsion, losing consciousness, and becomes unmanageable. This reaction goes on and on throughout the person's life. Holmes shows that what he describes is the result not of mere armchair philosophizing but of observation made at the bedside. He stated that possibly only through a shock similar to the one which the child encountered early in life or, as an alternative, through love, could this tendency be combated. Essentially that is what psychoanalysis tries to accomplish in each case, namely, to determine the point at which the deviation in a person otherwise normal has occurred. Usually this is far back in childhood; psychoanalysis then attempts to point out to the patient that the deviation was unnecessary, by tracing it to a point where resistance to normal progress developed. As Holmes grew older (he was 75 or 80 when the last novel was written), he had little of the zest or liveliness of a novelist and his writings took on more and more the aspect of a person looking back on his experience. He realized that the neurotic trends were due to unconscious mentation, and in that sense I should say that Holmes not only anticipated Freud, but presented clinical pictures not dissimilar to many of Freud's earlier reports.

NEW YORK NEUROLOGICAL SOCIETY

LEON H. CORNWALL, M.D., *President, in the Chair*

Regular Meeting, Dec. 3, 1940

Value of the Electrocardiogram in Metrazol Therapy. DR. LOUIS WENDER and (by invitation) DR. ABRAHAM JEZER.

We have studied the effects on the heart of metrazol administered in large doses in treatment of the affective disorders according to the technic introduced by Meduna. The convulsive dose varied from 3.5 to 13 cc. On a few occasions a dose had to be repeated, and 1 patient was given 27 cc. of metrazol within five minutes in order to produce a convulsion.

The effect of metrazol on the ventricular complexes of the heart was transient and of no clinical importance. No other changes were noted in patients who were observed during the first treatment or during subsequent treatment except for many changes in rhythm, which were as a rule sinus arrhythmias with varying degrees of depression of the sinus node. These findings were corroborated by similar observations reported by Bennett, McAdam and Forschbach. Repeated injections, in 1 instance three successive doses, failed to produce any changes worthy of note. The results were similar in more than 75 per cent of the cases. Fleeting changes following marked depression of the sinus pacemaker and stimulation of the auriculoventricular nodal pacemaker were present in about half of this group. A small number of the patients showed persistence of this arrhythmia for periods up to three minutes. Usually the nodal rhythm alternated with the sinus arrhythmia, resulting in gross irregularity of the heart rhythm. In 2 observations the arrhythmia was the result of partial heart (auriculoventricular) block. In 1 instance complete ventricular standstill for twenty seconds occurred soon after the convulsion. A similar observation was made by Forschbach. These arrhythmias are the so-called vagal arrhythmias and have also been observed during pneumoencephalographic procedures and after subarachnoid hemorrhage and cerebral accidents in patients whose hearts were normal. Since there are no changes in the ventricular complexes after the administration of metrazol and since the arrhythmias occur only after a convulsion, it is believed that the arrhythmias also are not of cardiac origin but result from stimulation of the extrinsic nervous mechanism of the heart. The effect on the latter is probably due to sympathetic-parasympathetic imbalance, with the parasympathetic influence predominating for several minutes after the convulsion. The rate of the heart usually increases to 135 to 180 beats per minute for one-half to one minute after the convulsion and then gradually falls to a more basic level after five to ten minutes. The amount of the drug given could not be correlated with the increase in the rate of the heart.

The following conclusions are drawn:

1. The repeated administration of metrazol does not produce any important change in the ventricular complex. There is a transient change in the S-T segment, which is the result of the increase in the heart rate and which usually disappears when the rate falls to a basic level.

2. There are no changes of any clinical importance which follow the injection of metrazol when no convulsion is produced.

3. When metrazol results in a convulsion three distinct types of arrhythmia may be produced.

   (*a*) Phasic sinus arrhythmia is the usual type and may or may not be accompanied by periods of sinus block.

   (*b*) A gross irregularity in rhythm is produced by the alternation of the normal sinus pacemaker and of the auriculoventricular nodal pacemaker in controlling the rhythm of the heart. The auriculoventricular nodal rhythm is due to sinus arrest.

   (*c*) On rare occasions heart block follows the convulsion induced by metrazol.

4. These arrhythmias are all manifestations of increased vagal influence and can be reproduced in susceptible human beings by the application of pressure on the carotid sinus by the administration of digitalis or by the induction of changes in intracranial pressure, such as follow subarachnoid hemorrhage and the injection of air for encephalographic study.

5. These changes are transient when produced by the convulsion following the administration of metrazol and have proved to be of no clinical importance in this series.

6. From the cardiovascular point of view there is no contraindication to the use of metrazol in the case of a patient with a normal heart or of a patient whose heart is mildly diseased.

7. These observations show that sinoauricular block, sinus arrest, sinus arrhythmia or auriculoventricular nodal rhythm, and occasionally heart block, may result from changes in the central nervous system rather than from changes in the heart muscle.

DISCUSSION

DR. MILTON J. RAISBECK (by invitation): This work is timely because the action of metrazol is not yet entirely known. It has been used as a stimulant to the circulation and the respiration, for indications that are not entirely clear and with pharmacologic effects which have not been thoroughly understood. Its use in the treatment of mental disease raises the question of possible harmful effects on structures other than the nervous system, and this contribution to the study of metrazol is helpful. It shows that the treatment need not be refused patients with the mistaken notion that the drug might injure the heart.

Previous observers have reported difficulty in securing graphic records because of tremor or other technical difficulties. Dr. Jezer and his associates must be complimented for overcoming these difficulties and presenting such an extensive series of graphic records to clarify this subject.

It has been reported that auricular fibrillation has occurred after the administration of metrazol. This has been confirmed by graphic records in a few cases. This type of fibrillation should not give one too much concern; it may occur in a young subject or one with an otherwise normal heart as a result of some extracardiac condition. This type of fibrillation should be easy to control with quinidine.

It is clear, however, from the material presented this evening that the irregularities following the use of metrazol may not be due to fibrillation, although they may simulate it. Variations in the level of rhythm of the active pacemaker in the heart and ectopic beats may produce an irregularity which would defy interpretation without graphic records. Such irregularities are benign and do not indicate an action on the heart which need be a cause of concern.

From the point of view of the cardiologist, the present studies demonstrate one point of great interest: the fact that block occurs, not only incipient block but actual dropped beats. It is the general impression that a block will not appear in the healthy heart as the result of vagus inhibition. In these subjects the heart was presumably healthy, and yet extracardiac factors were apparently adequate to produce block.

There appears to be no definite evidence of direct harmful action on the myocardium, as there are no significant changes in the T waves or the S-T segment. Most of the irregularities are distinctly benign, and, as I have noted, even fibrillation should not give one undue concern. This is the largest series so far reported on, and I believe that not a single instance of fibrillation is recorded. Therefore fibrillation must be rare under these circumstances.

In the absence of marked hypertension or evidence of organic changes in the heart, the exercise tolerance will remain a reliable method of estimating the degree of risk. If the patient shows normal exercise tolerance, ability to climb stairs,

and the like, without dyspnea or other manifestations of circulatory disturbance, the risk from metrazol therapy will be relatively slight.

DR. LEO L. ORENSTEIN: In 1938, at the meeting of the American Psychiatric Association held at San Francisco, I (*New York State J. Med.* **39**:1921, 1939) reported from the psychiatric service of Bellevue Hospital a small series of cases, 15 in all, in which this type of investigation was carried out. My collaborators and I were assisted in the interpretation of the electrocardiographic tracings by Drs. Battermann and DeGraff, of the cardiac service. I am glad to hear the presentation tonight, in which the authors report on a much larger group of patients and reach a similar conclusion as to the benignancy of the cardiovascular changes associated with metrazol therapy.

Abeles and Schneider (*Am. J. M. Sc.* **190**:673, 1935) pointed out the changes seen in the electrocardiogram in the course of encephalographic examination. Reports from other sources (Sands, J., and DeGraff, A. C.: *Am. J. Physiol.* **74**:416, 1925. Kountz, W. B., and Gruber, C. M.: *Proc. Soc. Exper. Biol. & Med.* **27**:170, 1929) suggest that anoxemia produces disturbances in the heart which are reflected in the electrocardiogram. Himwich and his associates (Himwich, H. E.; Bowman, K. M.; Fazekas, J. F., and Orenstein, L. L.: *Proc. Soc. Exper. Biol. & Med.* **37**:359, 1937) have shown that the oxygen content of the blood during metrazol convulsions drops to a very low level. I believe that the changes recorded in the electrocardiogram may be based partly on such anoxia, and I should like to ask Dr. Wender and Dr. Jezer to what extent they believe the low oxygen content of the blood is responsible for the changes they observed.

DR. ABRAHAM JEZER: In our series we were interested in the problem of anoxemia as it affects the electrocardiogram, particularly in the production of arrhythmias. After making our observations we are of the opinion that the arrhythmias are not due to the anoxemia of the heart muscle, since they may arise some minutes after the apneic phase is ended. It is at the end of this phase that the anoxemia is at its highest point.

We have shown such an electrocardiogram tonight. In this record the arrhythmia follows the end of the apneic phase by about a minute. There are no changes in the RS-T segment. The electrocardiogram in this instance fails to show any evidence of the effect of anoxemia on the heart muscle.

Electroencephalographic Changes Associated with Hypersensitivity of the Carotid Sinus. DR. SYDNEY G. MARGOLIN (by invitation), DR. HANS STRAUSS (by invitation) and DR. GEORGE L. ENGEL (by invitation).

Cerebral dysrhythmias associated with reflex vascular and metabolic disturbances were noted in a group of patients with pronounced neuropsychiatric manifestations. The first study is concerned with sensitivity of the carotid sinus as one of the etiologic mechanisms, though it is recognized that postural hypotension and vascular reactions to visceral stimuli (e. g., colonic or gastric distention) are analogous. Eleven patients were studied. On the basis of their histories and the results of examination they were divided into two groups. Five complained of inconstant weakness, dizziness, faintness and episodes of syncope. The other 6 exhibited objective signs of involvement of the central nervous system, such as focal or generalized convulsions, episodes of aphasia and sensory and motor disturbances. The reaction of the first group on stimulation of the carotid sinus was predominantly vagal and depressor. The response in these patients was abolished by atropine. The second group continued to manifest, even after administration of atropine, responses which were characteristic for each patient. In all cases, the chief complaint, namely the seizures, was duplicated. The sensitivity of the carotid sinus was examined with the patient lying down, sitting and standing. Three patients were discovered to have had postural hypotension, and corresponding enhancement of their responses in the standing position was noted. Attempts to produce sensitivity in this group by inflating the stomach and colon were unsuccessful.

Simultaneous electrocardiographic and electroencephalographic tracings and continuous sphygmomanometric records were obtained from each patient during stimulation, before and after administration of atropine. In all cases the spontaneous records were essentially normal.

On stimulation, the first reaction was hyperpnea, which continued throughout. Within a few seconds a diffuse and unlocalized burst of 4 per second waves of moderate potential appeared and persisted for a varying number of seconds, to be followed by a period of random low voltage activity. This was terminated by the clinical response of syncope or convulsion. When vagal depressor reactions were present, the dysrhythmia would appear after the pulse and blood pressures had returned almost to normal and the time of its appearance bore no relation to the duration of asystole. No clinical manifestation of carotid sinus sensitivity referable to the central nervous system became apparent unless the electroencephalographic cerebral dysrhythmia preceded it. The presence of the latter, however, did not always presage a discernible clinical response. Hence, the fact that the cerebral reaction to stimulation may be subclinical does not deny its presence.

The characteristic specificity of focal responses in the presence of diffuse dysrhythmia suggested that in these cases there was an underlying focal cortical diminution of threshold. Stimulation of the carotid sinus most likely provokes a generalized cerebral response, which, if it does not dominate the picture by syncope or generalized convulsion, makes manifest subclinical areas of cortical dysfunction. In this study, gross motor responses were used as indicators of such dysfunction. It is apparent, however, that investigation of other cerebral activities, such as visual field function, sensation, memory and intelligence, would reveal analogous disturbances.

Clinical Correlation of the Electroencephalogram with Carbohydrate Metabolism. Dr. George L. Engel (by invitation) and Dr. Sydney G. Margolin (by invitation).

In the preceding report we demonstrated a functional reaction of the central nervous system resulting from circulatory and reflex changes produced by stimulation of the carotid sinus. In this paper comparable reactions associated with disturbances in carbohydrate metabolism are discussed. The patients were grouped under the headings of exogenous and endogenous deficiency states, in which the defect particularly involved proper utilization of carbohydrates. In the groups with endogenous deficiency states, adrenal insufficiency was studied. Here, there is inefficient metabolism of carbohydrates due to lack of certain steroid hormones. The exogenous deficiency states were represented by patients with toxic-infectious diseases who had vitamin deficiencies and abnormal dietary habits. All of the patients presented a common denominator, namely, hypoglycemia and sustained profound neuropsychiatric disturbances. The latter were not characteristic and consisted of such manifestations as psychopathic behavior, excessive and inappropriate mood swings, impairment of insight and judgment, choreiform dyskinesias, convulsions, syncope, neuritic disorders and scotomas.

The fact that these patients all had hypoglycemia and that carbohydrate is the major metabolic substrate of the central nervous system provided the basis for this study. None of the patients in the groups with metabolic and vascular reflex disturbances had so-called idiopathic epilepsy or family histories of epilepsy. In all cases electroencephalograms made during fasting yielded cerebral dysrhythmias of diffuse slow high potential waves in bursts during hyperventilation. The standard procedure was to perform dextrose tolerance tests in the course of which electroencephalograms were taken simultaneously with hourly determinations of the blood sugar. During each record the patient hyperventilated for two minutes. The part of the hyperventilation period preceding the appearance of slow high potentials was called the induction period.

The results of these observations were uniform for all the patients studied. By calculating the number of seconds of slow high activity in a hyperventilation

period the percentage time of induction and the percentage time of dysrhythmia were determined.

After the ingestion of dextrose the amount of slow high activity during hyperventilation rapidly began to decrease, in some instances disappearing entirely. Then as the blood sugar levels began to fall there was a gradual return of the slow high potential, which reached its maximum at the lowest sugar level. This usually occurred four to five hours after administration of dextrose, and on a number of occasions there was a typical hypoglycemic reaction at this time, characterized by restlessness, sweating, tachycardia, abdominal distress and marked weakness. The reactions were generally ushered in by significant personality changes, the patient becoming uncooperative, abusive, apprehensive and sometimes dysarthric. In those instances in which hypoglycemic reactions were mild, blood sugar levels usually rose spontaneously and the slow high electroencephalographic activity diminished. The curve obtained by plotting hourly induction times against the duration of the experiment was found to parallel the dextrose tolerance curve and to exhibit a gross reciprocal relationship to the curve for slow high electroencephalographic activity.

The fact that cerebral dysrhythmia can be quantitatively related to variations of a metabolite is of great significance. First, it provides a method of investigating an as yet unexplained electrical cortical phenomenon. Second, the factors that influence the ultimate utilization of this metabolite, i. e., endogenous and exogenous mechanisms, are clarified in their etiologic relation to neuropsychiatric disease.

DISCUSSION OF PAPERS BY DRS. MARGOLIN, STRAUSS AND ENGEL

DR. ISRAEL WECHSLER: It seems to me that the authors have presented two important papers, both of which illustrate the intimate association between internal medicine and neurology.

There are several points to which one may allude. The concept of reflex epilepsy, which most neurologists have more or less discarded, may not be quite as false as is sometimes assumed. Naturally, I am not referring to reflex convulsions said to be the result of worms or phimosis or irritation of certain parts of the skin. The authors had in mind reflexes coming from the vascular system or the vasomotor system in various parts of the body which act on the brain to bring about convulsive discharge. In this sense reflex epilepsy is a tenable concept.

The patient of whom Dr. Engel spoke presented at one time what appeared to be an almost classic syndrome of a lesion in the body of Luys, namely, pronounced hemiballismus. It should be stated that before the advent of Addison's disease in this case the patient had thromboangiitis obliterans. When I first saw him he had, in addition, convulsions and speech disturbances. I thought of thrombosis of the corpus Luysi on the basis of thromboangiitis obliterans, which sometimes affects the brain. Only as I began to study the case did I learn that all of the symptoms were the result of hypoglycemia occurring in the course of Addison's disease.

Another important point is the relation of epilepsy, or the convulsion proper, to posture. Some may recall the presentation before this society by Dr. Bieber, Dr. Balser and myself of patients with convulsions which occurred only under certain postural conditions. For instance, a woman with a subarachnoid hemorrhage and a unilateral cortical lesion, had convulsions only when she lay on the side opposite the lesion. Another patient, also with a unilateral lesion, could prevent the convulsion if she could change her posture. If she had sufficient warning, she would by twisting her hand and turning her body stop the onset of the fit.

This leads to the question of the relation of posture and tonic neck reflexes to convulsions, and may throw light on why convulsions occur on going to bed and on arising. It is a common observation that patients frequently have convulsions immediately before or after falling asleep, that is, on going to bed, and it is even more common for patients to have convulsions on arising or just as they go to the bathroom immediately after awakening. Here is what one may speak of as a "sudden" change in posture from the erect to the horizontal on

going to bed, and from a prolonged horizontal position during the hours of sleep to a vertical one on arising in the morning. There may be some analogy here to postural hypotension and hypertension and to the fact that in cases of the carotid sinus syndrome convulsions vary with changes in posture. Usually they can be elicited better when the patient is in the sitting or the erect posture. Obviously, not all patients with carotid sinus sensitivity have convulsions. Some merely have attacks of syncope. There are several carotid sinus syndromes, and in only a few do convulsions occur. In some cases, however, in which one cannot elicit a convulsion with the patient lying down one may do so as he stands up. The posture in these cases apparently determines the onset of the convulsion. So far one cannot state that there is any localizing value in these tests.

I do not know whether Dr. Engel and Dr. Margolin are altogether right in saying that the abnormal waves they demonstrated in patients with hypoglycemia have nothing to do with epilepsy. Many neurologists have discarded the term epilepsy and have substituted the term convulsive state. The abnormal rhythms are similar, however, to those seen in cases of so-called idiopathic epilepsy. The important point is that during hypoglycemia patients have abnormal discharges, or dysrhythmias. One may speak of etiologic differences in physiologic changes, and in that sense distinguish these dysrhythmias from what in ignorance one calls idiopathic epilepsy. However, in favor of Dr. Engel's view one may point out that the hypoglycemic seizure is not quite like the tonic-clonic fit of "true" epilepsy. The patients go slowly into it; they slump, as it were, rather than have a sudden seizure.

Dr. Tracy Putnam: These papers are excellent examples of the way in which the encephalographic technic, and doubtless other precise physicochemical methods, may be used as a tool for solving complex physiologic problems. To me it is striking how the result obtained tends to simplify the problem, rather than to make it more complicated.

The results presented might well be used as an argument that there is no such thing as the pure cerebral or reflex type of syncope following irritation of the carotid sinus, for the sequence of events described for this condition is exactly that which one would expect to result from anemia of the brain, or of a part of it. The delay in the appearance of syncope after the asystole is just about the delay one would see if one clamped the carotid arteries instead of producing changes in the circulation. It is scarcely to be expected that the cortical cells would be starved out at once, and it is possible that once the abnormal rhythm is started it may maintain itself in spite of the fact that the circulation is reestablished. I do not feel that the changes in oxygen uptake offer a conclusive argument against the presence of partial anemia of the cortex, for this alteration is an index of metabolism of the entire brain and it is possible that the change is a local one which would be lost in the mass.

The observations on the various hypoglycemic states show a striking uniformity; irrespective of the other factors in the case, that of the blood sugar level appears to act in a fairly uniform and predictable fashion, at least as far as its relation to abnormalities in the electroencephalographic record is concerned. To be sure, there are different types of clinical response, but that is another story. Dr. Engel spoke of the tendency to consider specific wave forms as typical of epilepsy. I wonder if perhaps he was thinking of the point of view maintained so long by one of the pioneers in the field, Lennox, who is well known for his remark that epilepsy is a cerebral dysrhythmia. As far as I know, he has never committed himself to the idea that cerebral dysrhythmia is epilepsy. I think the first point of view is perfectly defensible; the second would indeed take one pretty far afield. It is obvious that there is an interesting field for investigation of the relationship between specific wave forms and specific clinical manifestations. Sometimes the correspondence is altogether uniform. One can look at a record and predict the clinical manifestations and vice versa, but with many wave forms, especially with indefinite types, one cannot be dogmatic.

Etiologic Relationship of Trauma to Schizophrenia. DR. A. A. BRILL.

Enough is now known about the cause of schizophrenia to answer the question whether it can be produced by a trauma, either physical or mental. Most of what has been said and written about this problem, from the time of Kraepelin until the present, answers this question in the negative. Yet civil cases are often brought to court in which it is claimed that a physical trauma, such as a fall or an injury, is responsible for the schizophrenia which is supposed to have developed after this particular injury. Two such cases are cited in which I gave testimony for the insurance company. In 1 case schizophrenia was supposed to have developed after a Colles fracture, and in the other, after a slight injury (bruises) to one of the knees. Investigation showed that both of the patients had always shown schizoid characteristics and had had schizophrenia long before these traumas occurred.

The question is still more important in relation to military service. The Veterans Administration Facilities have been caring for thousands of patients, most of them schizophrenic, at an enormous cost to the government, because it is presumed that the malady developed as a result of hardships in army service.

Numerous authorities, including Kraepelin, Bleuler, Hans W. Maier and many others, have denied this assumption. All of them have maintained, with Kraepelin, that schizophrenia is a primitive disease which is ubiquitous, that the same picture of schizophrenia which is found in European races is also found in the Orient, among the Chinese, Malays and other races. Kraepelin stated that in a preponderant number of cases the disease is entirely independent of external conditions of life, that schizophrenia is the outgrowth of a constitution and cannot be produced by external causes.

Bleuler, who devoted the best years of his professional life to the problem, expressed the same opinion. He repeated what has been frequently stated by Kraepelin and others, namely, that the first World War amply demonstrated that the worst hardships, the most intensive psychic traumas, as well as the cerebral injuries, have not produced any increase in the number of schizophrenic patients.

I agree with the authorities cited, and I feel that the time is appropriate for a discussion of the question, if possible, by a commission of experts.

DISCUSSION

DR. LOUIS CASAMAJOR: Dr. Brill has called attention tonight to what all psychiatrists know, and it cannot be reiterated too often, namely, that no one thing is the cause of schizophrenia. Schizophrenia is a gradual process, a process of development, and the causative factors, which Dr. Brill has described, are constitutional; they are so much the product of the personality and of the development of the organism that I question the propriety of speaking of schizophrenia as a disease. It is much more a type of reaction of the personality. In all cases the development of schizophrenia is extremely slow. There are cases in which the environment adjusts itself so gradually and so well to the needs of the schizophrenic personality that the symptoms appear in very slowly. There are others, however, in which the environment, for one reason or another, changes rather suddenly, and then the person, with his incapacity to react in what is called a normal way, shows schizophrenic symptoms more or less rapidly. Trauma, as Dr. Brill pointed out, is one of these factors of the environment; service in the army is another.

All know the boy or girl who is not able to get along in college and who blossoms out into a full-blown schizophrenic personality; then it is said that overwork at college was the cause. The true sequence is exactly the reverse. It is the person with the schizophrenic mind who finds it difficult to keep up normally in the environment of college and who finally breaks under it. Again, one frequently hears that the cause of the beginning of schizophrenia in a given case is the breaking up of a love affair—here, again, the sequence is the reverse. The fact is that the schizophrenic personality is unable to meet the needs of such an emotional

situation. Schizophrenia is a constitutional condition and forms a part of the personality development; eventually, either suddenly, with a change in the environment, or gradually, with the increasing inability of the person to adapt himself, the schizophrenic symptoms appear. The schizophrenia has been in existence a long time, but the outward expression of it has been kept under cover, to become obvious later according to the environmental situation which must be met.

DR. ISRAEL STRAUSS: Of course all agree that trauma cannot cause schizophrenia. Suppose, however, that Dr. Brill is testifying for the Industrial Commission and he is given the history of a patient who was working and was perfectly adapted to his employment; this man received a severe trauma to the head, which was followed in a short time by acute mental symptoms that were diagnosed as schizophrenia. There is, in addition, a history of a disposition which can be classified as that of a schizophrenic type. The referee asks: "Doctor, this man was working; you say he was schizophrenic, but he was economically self supporting. The trauma to the head occurred, and the man became completely disabled. Would you say that the trauma aggravated or precipitated the acute condition?" As psychiatrists, we are always asked: "Did the trauma aggravate the condition?" If we say "No," the referee asks how we should explain the sudden appearance of the psychotic symptoms which have completely disabled the man. If we admit that there may be some relationship between the sudden development of symptoms and the complete disability, then should not the patient be compensated for his disability as being the result of an accident?

I should like to ask Dr. Brill how he would meet that situation and do justice to both claimant and defendant.

DR. IRVING J. SANDS, Brooklyn: Dr. Brill has brought up an old problem which, because of the present draft law, has now assumed considerable importance. During the World War I served at the Port of Embarkation in New York, where all the so-called shell-shocked soldiers were returned from France. After the World War I was attending specialist in neuropsychiatry at the Veterans Hospital in New York (The Role of Trauma in Neuropsychiatric Diseases, *U. S. Vet. Bur. M. Bull.* **1**:32 [Sept.] 1925). I had to answer the very questions raised by Dr. Brill tonight. Furthermore, I have had the same problems confronting me in my treatment of patients under the Workmen's Compensation Law (Doctors, Lawyers and Injured Brains, *New York State J. Med.* **39**:2161 [Dec. 1] 1939). Of course, no physician who knows anything about schizophrenia, surely no trained psychiatrist, would say that trauma causes schizophrenia. However, the question is not asked in that manner. The psychiatrist is not asked by the referees whether the trauma has caused the schizophrenia, because they have learned that trauma does not cause it. What the psychiatrist is generally asked is in what way the trauma is associated with the patient's mental disorder, whether or not the trauma precipitated it. The word "precipitate" is being used more and more in the questions asked the expert.

While one understands schizophrenia clinically, no one has a real knowledge of its cause. In fact, I do not think anybody knows exactly what schizophrenia is. The best one can say is that it is a life reaction, which, once started, little can check. Despite the marked improvement noticed in many patients with the different forms of shock therapy introduced in the past three or four years, recurrences have been encountered. In other words, there is still doubt in many minds whether or not shock therapy can effect a real cure of this disorder. Therefore it is reasonable to say that the schizophrenic patient is a human being who is confronted with problems early in life which he cannot manage and to which he reacts with the behavior pattern that is called schizophrenia. Trauma elicits certain reactions, and therefore one cannot say that trauma may not precipitate a schizophrenic reaction.

May I illustrate my point with the following brief case history? A Puerto Rican in the late 30's is now a patient at the Kings Park State Hospital, where he is being treated for paranoid dementia praecox. Six years prior to the onset of his illness he had fallen a distance of some 20 feet (608 cm.) and had struck

his back. He could not walk, and he was removed to a hospital. He remained there for several months. On two occasions he was taken to the operating room, only to be returned to the ward without having had any surgical treatment. The insurance company was penalized on several occasions for not having sent the check due him. He persisted with his complaints. Once when he ran into a doctor's office demanding treatment, the doctor pushed him out of the office and the patient fell and had to be put to bed. His family was in want. For some eighteen months he complained that he was not getting a square deal from the company, that he had pains and that his condition was getting worse. Presently he began to complain that people were against him, were watching him and were trying to harm him and his family and he was finally committed to the state hospital. Can any one say that this patient's accident had nothing to do with the development of his psychosis? As psychiatrists, we were asked not whether his accident had caused the psychosis, but whether or not it could be dissociated completely from the psychosis. I doubt whether any one would say that the accident could entirely be dissociated from the development of this man's psychotic reaction. I question much whether a severe injury to the brain which was immediately followed by clinical schizophrenia had nothing to do with the development of the clinical picture of this serious psychotic reaction. Military service will not cause schizophrenia, but in military service there are many situations which may present difficulties and which if managed inadequately may precipitate schizophrenia. Trauma, therefore, may not be regarded as a cause of schizophrenia, but surely it may be a precipitating factor in its development.

DR. A. A. BRILL: I feel strongly on this problem. Suppose a house collapses, presumably because something bumped against it, and it is later shown that the house had been wobbly and dilapidated for some time and ready to fall to pieces at any time. Would you hold this slight bump responsible for the loss of the structure? I think not. The same thing applies to the cases cited. A patient who reacts in a schizophrenic manner is constitutionally schizophrenic. Dr. Strauss and Dr. Sands do not know that patients of the type they had in mind did not have schizophrenic episodes before they became manifestly schizophrenic as a result of a definite accident. Experience teaches that persons who have such a constitution can have schizophrenic episodes for one reason or another. The cause may be age, stress or accident; such persons simply cannot face the struggle in the normal manner. Once the schizophrenia becomes manifest it usually continues, with or without remissions. I purposely cited Hans Maier's case in which he considered the putative "precipitating cause" and recommended compensation for it, estimated at nine months. It shows that the psychiatrist need not be unmindful of the trauma. But Dr. Maier was careful to separate it from the fundamental disease. To be sure, if a person remained well past the age of 40, that is, past the dangerous period of schizophrenia, if that can be proved, and then sustained, say, a severe injury to the head which was followed by schizophrenia, one might say that the accident acted as a precipitating cause. But I should still maintain that even here neither the insurance company nor the government is responsible for the man's support for the rest of his life. I should consider such a case in the light of the student mentioned by Dr. Casamajor, who breaks down in school or college, an event for which "studying too hard" is blamed. Such a person is not equiped with the average constitutional makeup to start with.

I am glad that Drs. Casamajor, Strauss and Sands agree with the main thesis of my paper, namely, that schizophrenia is a constitutional disease and that once it starts, it goes on. I am convinced that trauma cannot produce it. Incidentally, I might add that trauma is not going to remove it, that shock therapies cannot remove the fundamental background. Many agencies, psychic and physical, can temporarily shock a schizophrenic patient into a new state of behavior, but experience shows that such reactions subside sooner or later and the patient returns to his original status. Nothing can remove a constitution once it is established.

It is immaterial whether, out of the kindness of one's heart, one wishes to help the poor patient financially. I have often felt that way in such cases, but such

emotionalism should not sway one into stating that the patient's malady is due to this or that trauma. I repeat that one might recommend compensation for the duration of the trauma, but one must be honest and separate it from the fundamental situation. One must not forget that no one has given more thought to the problem of schizophrenia than Kraepelin, Bleuler, Maier and the others whom I have mentioned.

CHICAGO NEUROLOGICAL SOCIETY

RICHARD B. RICHTER, M.D., *Councilor, in the Chair*

Regular Meeting, Dec. 19, 1940

Efferent Fibers of the Corpus Striatum. DR. S. W. RANSON and (by invitation) DR. S. W. RANSON JR.

This paper will be published in a later issue of the ARCHIVES, under the title "Fiber Connections of the Corpus Striatum as Seen in Marchi Preparations."

Multiple Primary Tumors of the Spinal Cord. DR. BEN W. LICHTENSTEIN.

This paper will be published in a later issue of the ARCHIVES.

Is the Hypothalamus the Seat of Emotion? DR. JULES H. MASSERMAN (by invitation).

As a result of certain misinterpretations of experimental and clinical data, there has recently arisen a tendency even among psychiatrists to stress unduly the role of the hypothalamus in the conative and emotional aspects of behavior. Examination of the evidence, however, leads to the following conclusions:

1. Experiments on animals have indicated that the hypothalamus may integrate and possibly reenforce the effector neural impulses controlling some of the sympathetic and motor manifestations of fear and rage; however, there is little or no basis for the thesis that the hypothalamus governs, or even mediates, the emotional experiences themselves.

2. Further work by my associates and myself has furnished evidence that a direct somatopsychic relationship between hypothalamic function and true affect does not exist, inasmuch as (*a*) the reactions induced by stimulation of the hypothalamus do not, within limits, greatly modify spontaneous emotional behavior, (*b*) animals with extensive hypothalamic lesions react to emotional stresses and can apparently experience genuine affective states and (*c*) animals subjected to prolonged conditioning procedures in which sensory signals precede direct hypothalamic stimuli do not learn to respond to either the sensory or the hypothalamic stimuli in ways analogous to their spontaneous or experimental adaptations to situations of adequate emotional significance.

3. The clinical and pathologic data on the role of the human hypothalamus in emotional experience are not conclusive.

4. It would, therefore, seem safest in the present state of knowledge to assign to the hypothalamus its experimentally demonstrable role in reenforcing and coordinating the neural and hormonal mechanisms of emotional *expression* and reserve for more adequate proof the hypothesis that it is either the dynamic source or the seat of experience of affective states. On the other hand, much experimental, psychologic and clinical evidence clearly indicates that an emotion is a highly complex conative and cognitive as well as affective state in which not only the central nervous system but the entire organism functions as a psychobiologic whole.

(The paper was followed by the presentation of a motion picture entitled "Experiments in Hypothalamic Conditioning.")

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

JAMES B. AYER, M.D., *Presiding*

Regular Meeting, Feb. 20, 1941

The National Emergency and Psychiatry: Civilian and Military Demands.
DR. C. MACFIE CAMPBELL.

The national emergency has already made a direct call on the services of many psychiatrists and offers a challenge to all psychiatrists, even those not at present directly involved.

In the work of the Selective Service System and in the induction of men into the army the psychiatrist has had to play his part.

The psychiatrist is interested not only in the selection of men for the army but in their training, and in the conditions of combatant service and resultant neuropsychiatric disorders. After induction the recruit has to face the problem of adaptation to an entirely new type of life, with removal from family, preoccupation as to family uncertainties, intimate life in common with a large group of new associates, novel restrictions, discipline and subordination, restriction of individuality and training in various technical activities. The period of adaptation has its own difficulties, and the psychiatrist can be of use in close association with the medical officers and the line officers in detecting indications of vocational unsuitability on the part of the recruit and indications of personal difficulties which require attention and treatment. Rivers has suggested the possibility that the training and discipline, by restricting individuality, may increase suggestibility and therefore perhaps foster the development of hysterical symptoms during combatant periods. The psychiatrist, by talks to the soldiers and officers on mental hygiene and the nature of war neuroses, may promote the morale of the unit and reduce the incidence of war neuroses.

While the army takes responsibility for following up the men selected by the Selective Service System, the psychiatrist is interested in the requirements of the civilian community at large, including those rejected by the Selective Service System. The army can attain maximum efficiency only if honestly supported by the civilian community. Morale in the factories is as important as morale in the army. The human difficulties with which the psychiatrist deals may express themselves in labor unrest, class hostility, racial antagonisms, personal vituperation, panicky reactions, apathy or defeatism, waste and disorganization. Community conditions neglected in peacetime have a chance of receiving more adequate attention in a time of national emergency.

The interest of the army in the personal equilibrium of the individual soldier, in his vocational training and in the establishment of sound personal bonds between him and the group should be supplemented by an equal interest of the civil authorities in the mental hygiene of the community at large, in the development and maintenance of a wholesome social solidarity.

The general program of mental hygiene, which in peacetime excites a lackadaisical interest, may well receive strenuous backing in this time of national awakening. This program includes the development of adequate facilities for the early recognition, care and treatment of personality disorders in the community. This requires the cooperation of general practitioners, medical societies and medical schools. It includes attention to the mental hygiene of the home, with a survey of the actual resources available for this purpose—medical and nursing personnel, family welfare and children's agencies, habit clinics, settlements, and so on. It stimulates the school system to assimilate the principles of mental hygiene and, through education of teachers in knowledge of childhood psychology, to prepare the children much better for life.

In occupational groups, in industry and commerce, in the large factories, stores and offices, there are opportunities for taking stock of civilian morale, for scrutiniz-

ing the conditions of the individual life and for helping to promote a sound group spirit within the factory or store or office which will foster a still wider and more generous cooperation with the community at large.

Apart from these major groups, there are in every community a great number of groups associated in accordance with religious, racial, cultural, esthetic and athletic interests which may be centers for useful stimulation or indoctrination.

The extent of the problem is considerable, but the facilities for dealing with it are also considerable. State departments of mental health and of public welfare, school systems, the churches, the press, the radio, offer important resources. The psychiatrist is interested in seeing these resources mobilized to deal with the mental hygiene of the community, so that the home front may be as efficient as the combatant front.

Effect of Amphetamine Sulfate and Allied Drugs on the Alcohol Level of the Blood. Dr. Max Rinkel and Dr. Abraham Myerson.

The effect of amphetamine (benzedrine) sulfate in the treatment of alcoholism is twofold: (1) It stimulates the central nervous system, and (2) it inhibits the concentration of alcohol in the blood. On the basis of its central stimulating effect, Bloomberg has successfully utilized this drug in the treatment of chronic alcoholism. His work has been confirmed by our own clinical experience. Reifenstein and Davidoff (*New York State J. Med.* **40**:247, 1940) suggested the use of amphetamine sulfate in the treatment of acute "pathologic intoxication" on the assumption that the drug may produce its beneficial effects "directly by neutralizing and antagonizing the alcohol itself." This assumption was not based on experimental data and is not correct, as our studies have shown.

In the course of our investigations on the pharmacologic reactions of the autonomic nervous system, we studied the relation of amphetamine sulfate and alcohol concentration in the blood in man and in animals. We also included in our investigations such chemically and pharmacologically related drugs as hydroxyamphetamine (paredrine), epinephrine and atropine sulfate.

The results of our studies may be summarized as follows: If amphetamine sulfate is given in amounts ranging from 30 to 40 mg. intravenously, or from 20 to 40 m. orally, the concentration of alcohol in the blood following oral administration is markedly depressed. The same effect may still be observed seventy-two hours after the administration of amphetamine sulfate when this drug is protected against quick absorption. At the suggestion of one of us (Dr. Myerson), amphetamine sulfate was dissolved in gelatin and injected intramuscularly. The result was a marked depression of the concentration of alcohol in the blood, similar to the immediate results obtained when amphetamine sulfate dissolved in sterile distilled water was given—with this exception, however, that the aqueous solution of amphetamine sulfate was no longer active at the time when the gelatinous solution still had its full effect. Essentially the same result, but to much less degree, is obtained with hydroxyamphetamine (paredrine), epinephrine and atropine. Amphetamine sulfate is the most effective drug, its influence on the concentration of alcohol being not only greater at any given time but of longer duration. Hydroxyamphetamine (paredrine) ranks second in effectivity and epinephrine third. Atropine seems to be the least effective of these drugs.

In the interpretation of these results, it was established experimentally that the inhibition of the alcohol concentration in the blood was due solely to decreased absorption of alcohol from the gastrointestinal tract. This conclusion is corroborated (1) by the shape of the experimental blood alcohol curve, which shows a gradually ascending slope, in which the peak has been shifted to the right as compared with the control curve; (2) by the equal inhibition of the alcohol concentration in the arterial blood; (3) by the absence of an effect when amphetamine sulfate is given at the height of the absorption of alcohol; (4) by the lack of any appreciable alteration of the blood alcohol curve when alcohol is injected intravenously, absorption from the alimentary tract being thus excluded, and (5) by

the clinical observation of the influence of amphetamine sulfate on the intoxicating effect of large amounts of alcohol.

For these experiments pigeons were used: Two pigeons, A and B, of about the same size and weight, each received by tube 3 Gm. of alcohol per kilogram of body weight. Pigeon B received an additional intramuscular injection of 1 mg. of amphetamine sulfate per kilogram of body weight. While the control pigeon, A, collapsed within twenty-five minutes after the administration of alcohol, pigeon B, which was given the injection of amphetamine sulfate, did not seem to be affected. Four hours later the effect was reversed: Control pigeon A recovered, while experimental pigeon B collapsed.

Factors other than absorption which influence the alcohol level in the blood, such as excretion of alcohol through the lungs and urine, oxidation and diffusion, may be excluded in explaining the inhibition of the alcohol concentration in the blood in our experiments. There is no evidence for the assumption of Reifenstein and Davidoff that amphetamine sulfate neutralizes and antagonizes the alcohol itself. The drugs the actions of which were studied in these experiments merely delay the absorption of alcohol. Their application in the treatment of acute pathologic intoxication, therefore, cannot be unreservedly recommended, and they should not be used while a person is still drinking.

Further Report on the Use of Amphetamine (Benzedrine) Sulfate as an Adjuvant in the Treatment of Alcoholism. DR. WILFRED BLOOMBERG.

Fifty-five cases of chronic alcoholism in which the patients were treated with amphetamine sulfate, as well as by psychotherapy and other methods, are reported. The patients have been followed from periods ranging from a few weeks to three and three-fourths years. The results in general have been approximately the same as those reported in the first series of 21 cases; that is, about 25 per cent of the patients have remained totally abstinent, and between 80 and 85 per cent of those treated have undergone significant modification of their drinking habits.

Amphetamine, by relieving the chronic "hang-over" and depression of the chronic alcoholic patient during the period of withdrawal, is a useful aid to any form of treatment. It assists in establishing rapport with the patient and makes him feel that something concrete is being done for him.

It is concluded that whatever methods of treating chronic alcoholism are employed, amphetamine is of great assistance thereto.

Alcoholism: Some Contemporary Opinions. DR. MERRILL MOORE.

This article appeared in full in the April 1941 issue of *Mental Hygiene* as a brief report of a three day symposium conducted by the Research Council on Problems of Alcohol at Philadelphia, Dec. 27 to 29, 1940, under the title "Alcoholism and the Alcoholic."

DISCUSSION ON PAPERS ON ALCOHOLISM

DR. ABRAHAM MYERSON: It seems to me that in the use of alcohol in particular, the social attitude is the most important factor. Whatever is done with chemical substances or with vitamins is done after the damage is inflicted. Drinking should be a matter of social education. Alcohol has a prime communal use as an aid to social fellowship, and it is used in religious communion. Because this social value was not taken into account prohibition failed, and I believe prohibition is not desirable. Unfortunately, as I have pointed out, the ability to take alcohol has become a measure of the person's worth. Inability to drink has become a symbol of lack of virility. This attitude has to be corrected by a well planned educational program, directed particularly toward the youth of the community and toward the liberal institutions in which youth congregates.

The place of alcohol as a drug has not been sufficiently stressed. Alexander, Moore and I believe that it is time that alcohol be placed under the control of

the federal Food, Drug and Cosmetic Act. If a manufacturer falsifies the vitamin content of a food he can be hailed before the courts and punished. If a person who sells a narcotic drug fails to put a warning label on it, he, too, is violating the Food, Drug and Cosmetic Act and is liable to punishment. By definition of the United States Government, alcohol is both a food and a drug. The Pharmacopeia of the United States includes alcohol in many places. If a man buys whisky, he has a right to get whisky. Most whiskies are grain alcohol colored, improved perhaps by a blend of whisky, but are not really whiskies according to the definition in the Pharmacopeia.

We advocate that if the federal Food, Drug and Cosmetic Act does not apply to alcohol, then it should so apply. Part of the need in the social situation seems to be to have alcohol stand for what it is—a valuable substance under circumstances of temperance. It is a dangerous drug otherwise. Consequently, the medical profession should be for temperance and should fight for a better social attitude toward the use of alcohol. Placing its sale, branding and advertising under the provisions of the federal Food, Drug and Cosmetic Act seems to us an effective and desirable form of social medicine.

DR. IVES HENDRICK: Dr. Bloomberg seems almost to prove his point, that amphetamine in his hands is a valuable adjuvant in stabilizing his alcoholic patients. This must surprise most physicians, who find alcoholism the most difficult of psychiatric problems. Will Dr. Bloomberg explain how amphetamine produces therapeutic effects? Is it through the mild, drug-induced euphoria which enables the alcoholic patient to get through his depression without going under? Dr. Moore has brought home statistically, in the introduction of his paper, the tragedy of those who succumb to alcohol. But one must be careful not to draw a misleading conclusion from this, for such figures easily entice one into thinking that this tragedy is primarily a consequence of alcohol. Thus one would follow the example of many alcoholic addicts themselves in blaming the disasters of their lives entirely on the stimulant. One would thus overlook the more important fact, which is justified by psychiatric knowledge of the problem, that had alcoholic psychopathy not developed, most of these persons would have succumbed to disaster in some other way. Alcoholism is a disaster, but it is a symptom, not a cause. I therefore do not concur with Dr. Myerson's premise that the problem of alcoholism should begin with the recognition that alcohol is a drug, or with his optimism in attacking it as a social, rather than an individual, problem. Of course alcohol is a drug, and directly and indirectly damages the body in well known ways. But it is not the drug which starts the cycle. Dr. Myerson pointed out the strange fact that imbibition is commonly esteemed a proof of virility. Gonorrhea is similarly esteemed by the adolescent minded. Such attitudes are widespread; they are nonetheless clearly neurotic, for they are fantasies which contradict reality and gratify harmfully a frustrated desire to be adult and masculine. But there are still clearer indications that alcoholism is a neurosis, that the alcoholic person is extraordinarily and fundamentally infantile in many other ways. Most alcoholic addicts continually lie, and what is particularly striking is that they lie in ways harmful to themselves. They all have an exorbitant need for affection and praise. They generally encounter disastrous failures, even when their successes have been temporarily of a high order. They constantly stimulate raillery and abuse, even from usually stable and sensible companions. This is commonplace knowledge and leads one to expect that neither appeal to their intelligence nor social pressure will solve their problems. I do not discourage the study of the sociologic aspects of alcoholism; it is an important approach. But I discourage the attitude that this can supplant prolonged psychiatric investigation of the psychogenic factors in individual cases. Dr. Myerson's and Dr. Moore's suggestion that whisky be labeled a dangerous drug is worth trying; it might sometimes prove a useful caution to the intoxicated normal driver, but it would never help an alcoholic one.

DR. WILLIAM G. LENNOX: The problem of alcoholism provides the opportunity for doing that which Dr. Campbell urged, namely, placing the influence of

the society behind practical problems of the community, of which alcoholism is one of the greatest.

DR. M. RALPH KAUFMAN: I should like to ask Dr. Bloomberg whether he has a control series of alcoholic patients who were treated without amphetamine, and, if so, what the results were. Dr. Bloomberg's personality may play some part in his marvelous results.

DR. WILFRED BLOOMBERG: In answer to Dr. Hendrick: I have no idea how amphetamine works in alcoholism, or indeed in narcolepsy, except that its action is on the central nervous system, and not on the periphery. My ideas about this mechanism are too complex to be discussed at this time, and in any case are largely inferential and theoretic, rather than based on experimental fact. I think that when the chronic alcoholic patient is given amphetamine the first effect is enormous relief of the deadly depression and "hang-over" that go with withdrawal. Curiously also, amphetamine seems to diminish the severity of "jitters" and to produce sleep.

In reply to Dr. Kaufman: I have already said that these results are not suitable for statistical analysis, since the cases are too few and the methods of treatment used in addition to administration of amphetamine vary markedly. Some patients were psychotic or psychoneurotic, and others were not. The only controls available are those mentioned in the published reports on other technics. It should be noted that no claim has ever been made that amphetamine is a cure for alcoholism. It has only been said that the drug is a useful adjunct to whatever other treatment these patients receive.

As to the psychologic technics involved, I find my ideas in disagreement with those of many other therapeutists of alcoholism. For example, I do not believe in institutional treatment if it can be avoided, and I am convinced that one should not be a defeatist and insist that the alcoholic addict consider himself different from other people. However, this is not the place to go into this aspect of the situation.

DR. MERRILL MOORE: The remarks of Dr. Hendrick are extremely pertinent. In regard to ambivalence in alcoholic patients, attention is called to Dr. Myerson's article in the June 1940 issue of the *Quarterly Journal of Studies of Alcohol.*

Because of lack of time, I was unable to report adequately on many of the papers of the symposium or to give some of the more interesting opinions. But I should be the first to agree with Dr. Hendrick concerning the importance not only of prolonging an intensive study of alcoholic addicts, but also of investigating the personality at all levels and by all technics. It has been said that as little is known about alcoholism as was known about diabetes thirty years ago. It is still felt that the investigation of the alcoholic personality offers an alluring opportunity for exploration.

Book Reviews

Science and Seizures: New Light on Epilepsy and Migraine. By W. G. Lennox. Price, $2. Pp. 247, with illustrations and index. New York: Harper & Brothers, 1941.

This book is difficult to classify. It is evidently addressed to the laity and contains a great deal of information likely to be useful to patients suffering from epilepsy and migraine and to their relatives. This does not represent its entire appeal, however. Many intelligent nonmedical readers who have no personal concern with the subject will develop an abstract interest in it through this volume. The book has a dramatic as well as an intellectual side, and devotes much space to the historical and economic aspects of seizures, as well as to more purely medical considerations.

Physicians also will find much that is new and of value in this book. It records the results of the extensive statistical investigations carried out by the Boston group over the past half-dozen years. Much of this material is of great potential importance in understanding of the problem of epilepsy. The chart on page 55, for example, gives for the first time convincing proof that "repeat" seizures tend to cause intellectual deterioration. The author's open-minded approach to the problem and the many bits of practical wisdom which has grown from long experience might serve as a guide to all who come into contact with the disorder.

Not all authorities will agree with the opinions expressed. The results of treatment of convulsions by surgical measures and by dehydration are estimated at rather low worth. The existence of an allergic tendency in migraine is viewed with skepticism. The value of electroencephalographic studies in the understanding of the disease process and in diagnosis is strongly emphasized.

This is a book which physicians will want to recommend to patients, but not without discrimination. It presents a rather grim picture of the problem, and there are many parts of it which will be difficult for patients to understand. Few readers can, however, fail to be impressed by the spirit of courage and determination which shows on every page. The literary style has a peculiar charm and appeal which makes easy reading. The author proposes to donate the profits from the sale of the book to scientific purposes.

Hydrocephalus: Its Symptomatology, Pathology, Pathogenesis and Treatment. By Otto Marburg. Price $3. Pp. 217. New York: Oskar Piest, Inc., 1940.

This little book contains an interpretation rather than a review of the literature on hydrocephalus, the interpretation being largely in terms of the author's own viewpoint in connection with this disease. This viewpoint has apparently changed in recent years, since the author, who previously believed in the generally accepted theory that hydrocephalus is usually associated with an obstruction to the cerebrospinal fluid spaces, whether it be within the ventricles or at the point of absorption of the cerebrospinal fluid into the venous system, is now of the opinion that hydrocephalus is a "disturbance of water metabolism." "More fluid than normal enters into the brain and reabsorption is also affected, both conditions being caused by a disturbance of permeability of the hemato-encephalic barrier." As an example of this change in point of view, one may cite the author's complicated attitude toward his own belief in the efficacy of roentgen irradiation in the treatment of hydrocephalus. He still believes, as he did in the past, that this form of therapy is efficacious, but while he formerly explained the efficacy by the effect of the roentgen radiation on the choroid plexuses, he now explains it by its effect on the blood-brain barrier.

Some of the interpretations of the extensive literature on the subject of hydrocephalus, to bring it in harmony with Marburg's latest point of view, appear considerably strained. After completing the volume, one is left in a state of confusion, not only by the too literal translation of the book, which apparently was originally written in German, but also by uncertainty in regard to the author's actual conception of hydrocephalus.